

**'Studies Directed Toward the Synthesis of the
Galbulimima belgraveana Alkaloids'**

A Thesis submitted for

the Degree of

Doctor of Philosophy

at

The Research School of Chemistry

of

The Australian National University

by

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May 2002



Declaration

This Thesis contains no material previously submitted for a degree in any other University, and to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference is made in the text.

A handwritten signature in black ink, appearing to read 'M Murdoch McLachlan', written in a cursive style.

Matthew Murdoch McLachlan

'The first public laboratory I worked in was the Royal College of Chemistry in Oxford Street, London, in 1853-1856.' It wasn't like the great electric laboratories of today, he noted, with your huge booming furnaces. 'There were no Bunsen-burners - we had short lengths of iron tube covered with wire gauze.' It was a grey place. There were many nasty explosions.

Simon Garfield, "Mauve" Quoting Sir William Perkin

Acknowledgements

First and foremost, I would like to thank Lew Mander for his dedication to the Mander group and the supervision of this thesis. Lew's intellectual input to this thesis and his ability to remember every paper of any relevance ever published (and the journal and page number to find it) is greatly appreciated.

I must also thank the members of the Mander group who have shared their time at the RSC with me. In particular I must thank Regan Thomson for his friendship over the years, the many helpful discussions we have had over a quiet beer at the pub, and the many unhelpful discussions we have had over a loud beer at the pub. Thanks also to Ollie Hutt, Patrick O'Connor, Kelly Fairweather and Le Thanh Phuoc for their friendship over my time at the RSC.

A special note of thanks also to the support personnel who have helped with all the technical difficulties that must be overcome in the course of this research project. In particular Bruce Twitchin, for general lab support, Chris Blake, for help with running NMR spectra, Dr. A. C. Willis, for X-ray data, and Tony Herlt, for helping when needed most.

I also thank the people who have shared my house with me during my stay in Canberra, Karyn Thompson, Leah-Kate Hannaford, Pascal Geier, Sally Quatermaine and Sam Tingey. They made me feel at home, and they taught me that art and science are two sides of the same coin.

To my family: Peter Woodhead, Kennedy McLachlan and Justine McLachlan, thank-you for your support and encouragement through the years.

Grateful acknowledgment is made to the A.N.U PhD scholarship, the A.N.U graduate school scholarship and the Frank Sargeson scholarship for financial support.

Last but not least I must thank Rachel Hannaford for her never-ending love and support, particularly through the last trying months of this PhD.

Abstract

This thesis explores a synthetic approach to the alkaloids GB 13, himbadine, himgaline and related members of the himandridine family of alkaloids. These compounds had been previously isolated from the North Australian and Papua New Guinean rain forest tree *Galbulimima belgraveana*.

A Birch reductive alkylation of 2,5-dimethoxybenzoic acid by 3-methoxybenzyl bromide, followed by an acid catalysed cyclisation was used to synthesize the [3.3.1]bicyclononane (5RS,9RS)-5,6,7,8,9,10-Hexahydro-5-hydroxy-2-methoxy-8-oxo-5,9-methanobenzocyclooctene. A ring contraction performed on a derivative of the [3.3.1]bicyclononane lead to the [3.2.1]bicyclooctane (5SR,7SR,8RS)-Methyl-6,7,8,9-tetrahydro-2-methoxy-5-methoxymethoxy-5,8-methano-5H-benzocycloheptene-7-carboxylate, which was envisaged as an intermediate common to the preparation of all of the target alkaloids. This [3.2.1]bicyclooctane was converted into a dienophile and subjected to a Diels-Alder reaction to generate a pentacyclic intermediate with a carbon skeleton closely resembling the target alkaloids GB 13, himbadine and himgaline.

Methods for the removal of a surplus carbon from a quaternary center were explored next, with the most successful route being the use of Birch reductive conditions to effect a decyanation. It was discovered that a Birch reduction of an aromatic ring also present on the molecule could be performed at the same time to give an enone, which was suitable for further elaboration towards the target compounds.

The synthesis was subsequently revised to improve efficiency, with the result that the synthesis was shortened by several steps and the overall yield improved. Then the cyclic enone formed after the Birch reduction was cleaved by a variety of methods to give keto derivatives, which were used to

explore the synthesis of the piperidine ring found in the natural products. The final chapter in this thesis discusses the future potential of this work to synthesise the alkaloids isolated from *Galbulimima belgraveana*.

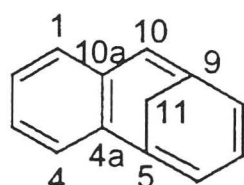
Abbreviations

Ac	Acetyl
APT	Attached proton test
Ar	Aryl
Bn	Benzyl
BOC	<i>tert</i> -Butylcarbamate
Bu	Butyl
Bz	Benzoyl
c.	Concentrated
<i>m</i> CPBA	<i>meta</i> -Chloroperbenzoic acid
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-Dichloroethane
DCM	Dichloromethane
dil.	Dilute
DIPEA	Di- <i>iso</i> -propylethylamine (Hunig's base)
DMAP	4-(Dimethylamino)pyridine
DMDO	Dimethyldioxirane
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
EI	Electron impact
Et	Ethyl
FMO	Frontier molecular orbital
H	Hydrogen
HOMO	Highest occupied molecular orbital
h ν	Ultraviolet radiation
IR	Infrared
<i>J</i>	Coupling constant
KDA	Potassium di- <i>iso</i> -propylamide
LAH	Lithium aluminum hydride
LDA	Lithium di- <i>iso</i> -propylamide
LUMO	Lowest unoccupied molecular orbital
M	Mol per litre
Me	Methyl
MHz	MegaHertz
MOM	Methoxymethyl
NMR	Nuclear magnetic resonance
P	Protecting group
PCC	Pyridinium chlorochromate
Ph	Phenyl
ppm	parts per million
PPTS	Pyridinium <i>para</i> -Toluenesulfonate
¹ Pr	<i>iso</i> -Propyl

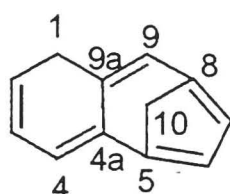
Py	Pyridine
R	Substituent
TBAF	Tetrabutylammonium fluoride
TBS	<i>tert</i> -Butyldimethylsilyl
Tf	Triflate
thd	2,2,6,6-tetramethyl-3,5-heptanedionate
THF	Tetrahydrofuran
THP	Tetrahydropyranyl
TLC	Thin layer chromatography
TMS	Trimethylsilyl
Ts	Tosyl
<i>p</i> TSA	<i>para</i> -Toluenesulfonic acid

Notes on nomenclature

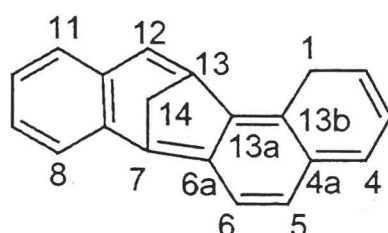
The nomenclature system used in this thesis conforms to the indexing policies of the Chemical Abstract Services (CA index Guide), which are generally in accordance with the rules published by the International Union of Pure and Applied Chemistry (IUPAC). The base structures for the compounds named are presented below.



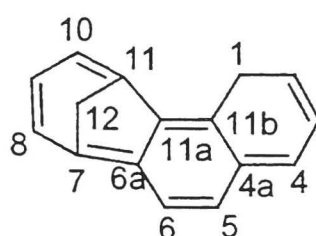
5,9-methanobenzocyclooctene



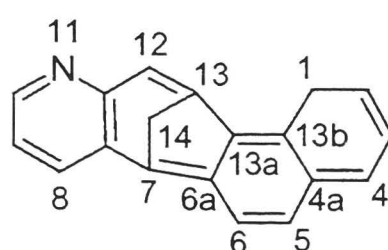
5,8-methano-1*H*-benzocycloheptene



7,13-methano-1*H*-benzo[4,5]cyclohepta
[1,2-*a*]naphthalene



7,11-methano-1*H*-cyclohepta[*a*]naphthalene



7,13-methano-1*H*-naphtho[2',1':4,5]cyclohepta
[1,2-*b*]pyridine

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Chapter 1

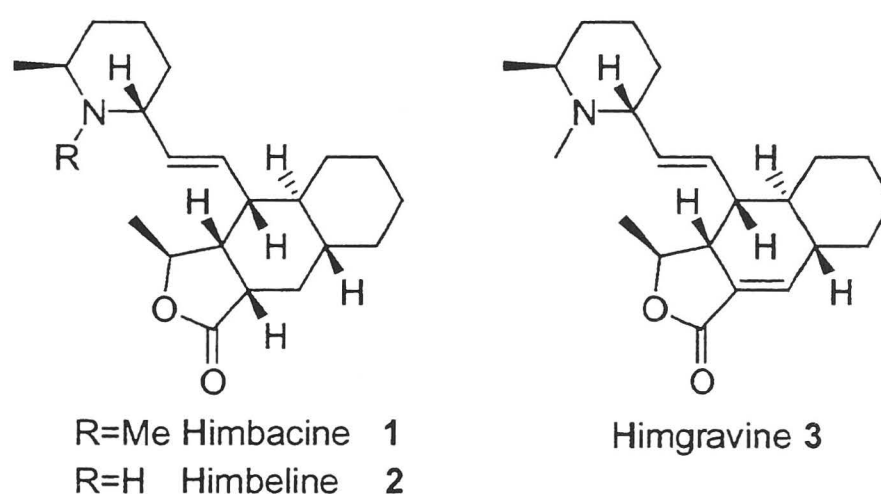
Introduction

1.1 Introduction

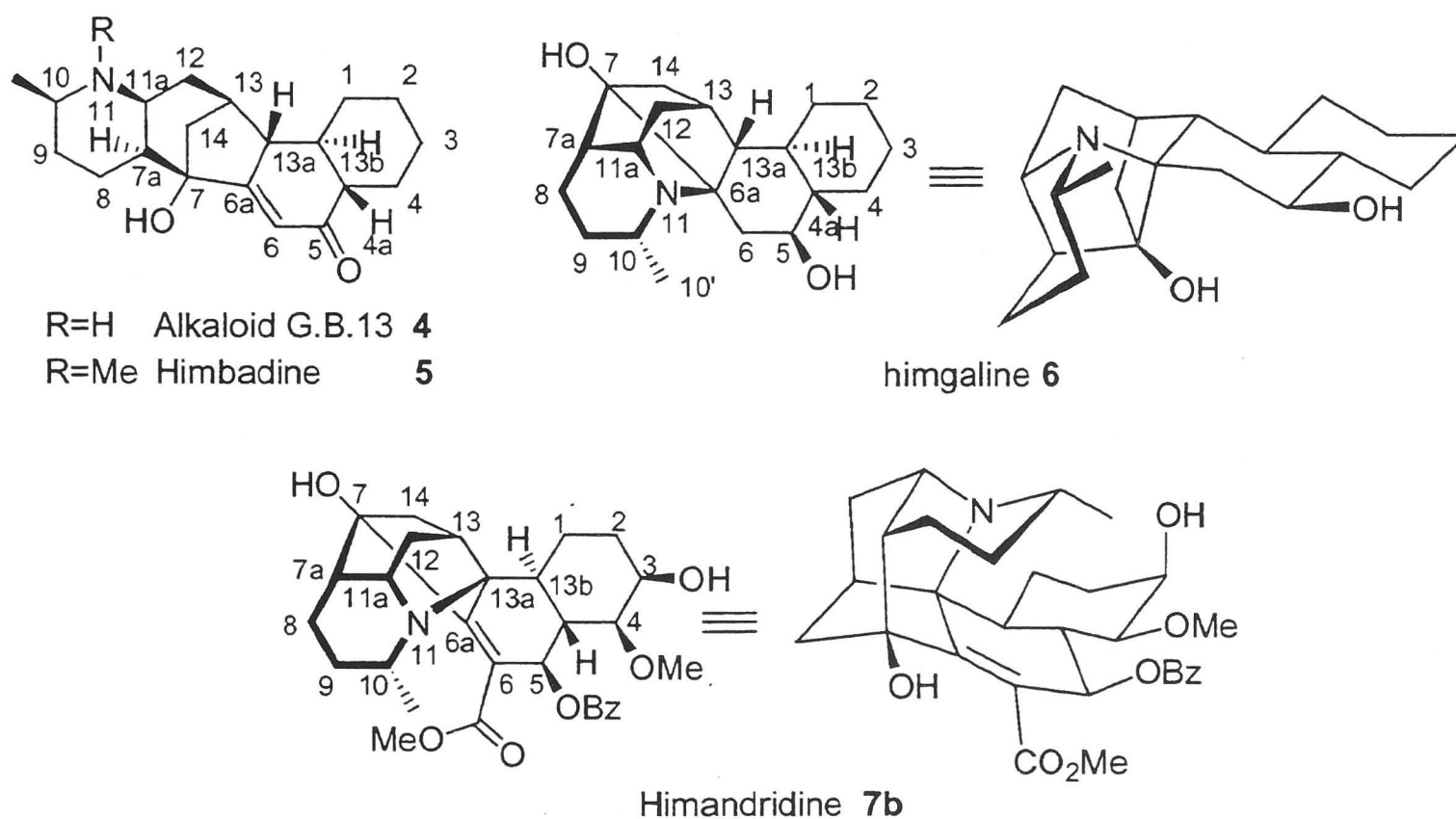
The rain forest tree *Galbulimima belgraveana* is found in Northern Australia and Papua New Guinea, and is the sole member of its relic family, Himantandraceae. The bark of *G. belgraveana* has been used as a medicinal substance by some Papua New Guinean tribes for a variety of purposes.¹ The Fore people use the bark of *G. Belgraveana*, occasionally in combination with other plants, in rituals to make young men fierce. The Gimi people use the bark to produce trance-like states and visions, while the Oksapmin people use a combination of the bark and wild ginger to treat diseases attributed to sorcery and witchcraft, such as fever, skin conditions and poisoning. It has also been reported that the Aseki people use the chewed bark mixed with salt as an analgesic.

The leaves and wood of *G. belgraveana* are alkaloid poor, and have not been examined in any depth. However, the bark is rich in alkaloids and to date a total of 28 unique alkaloids have been isolated from this source.^{2,3} The variety and total amount of alkaloids isolated from individual samples is highly variable, even when season and locality are taken into account. The alkaloid content of the bark can range from trace amounts, up to 0.5% by weight. Only a few of the alkaloids are common to all samples tested, the rest of the alkaloids occurring irregularly and often in trace amounts.

This family of alkaloids can be divided into two broad categories based on the carbon skeleton. The first category has a planar structure and is represented by himbacine (1). Other members of this family are himbeline (2), himgravine (3) and himandravine, which has the same structure as himbeline (2), but unknown stereochemistry about the piperidine ring.



The second category has a bridged carbon skeleton: e.g. alkaloid GB 13 (4) and himbadine (5). Some of the bridged alkaloids are further folded into a hexacyclic cage structure such as himgaline (6) and the highly oxygenated ester family of alkaloids (Table 1.1) represented by himandridine (7b).



Most of the isolated alkaloids have some pharmacological activity, characterised by inhibition of the parasympathetic nervous system,⁴ both systemic and within the central nervous system. This inhibition results in the observed physiological effects of hypotension, bradycardia, and muscle relaxation, as well as less readily characterised psychological effects.

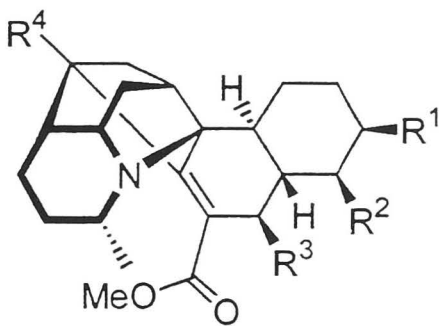


Table 1.1: Variations on the substitution patterns of the himandridine family of ester alkaloids

	Alkaloid	R ¹	R ²	R ³	R ⁴
7a	Himbosine	OAc	OCOPh	OAc	OAc
7b	Himandridine	OH	OMe	OCOPh	OH
7c	Himandrine	H	OMe	OCOPh	OH
7d	G.B.1	OAc	OCOPh	OAc	OH
7e	G.B.2	OAc	OAc	OAc	OAc
7f	G.B.3	OAc	OH	OH	OAc
7g	G.B.4	OCOPh	OH	OH	OAc
7h	G.B.5	OH	OH	OH	OAc
7i	G.B.6	OAc	OMe	OCOPh	OH
7j	G.B.7	OH	OMe	OCOPh	OAc
7k	G.B.8	H	OMe	OH	OH
7l	G.B.9	H	OMe	OAc	OH
7m	G.B.10	H	OMe	OAc	OAc
7n	G.B.11	H	OH	OH	OAc
7o	G.B.12	H	OAc	OAc	OAc

Himbacine (1) has been identified as the most promising lead compound for the treatment of Alzheimer’s disease from this family of alkaloids, and has been relatively well studied. Structure activity relationship studies carried out on himbacine have shown that the tricyclic lactone and the N-methyl group are essential for selectivity and potency. Himbacine has been shown to have a 10-fold selectivity for the M₁ class (K_i = 4.5 nM) over the M₂ class (K_i = 48.4 nM) of muscarinic acetylcholine receptor.^{5,6}

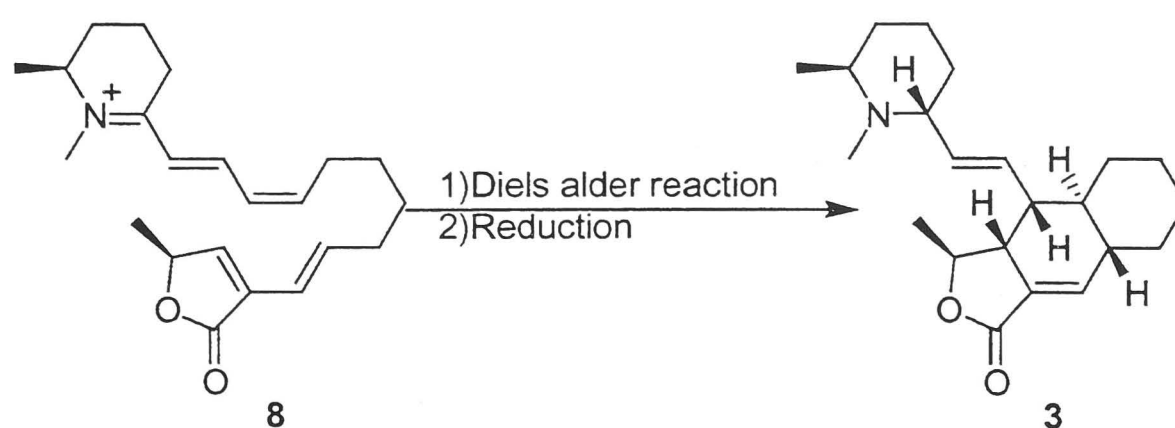
Within the central nervous system, inhibition of the presynaptic M_2 receptor prevents feedback inhibition of acetylcholine release resulting in an increase of synaptic acetylcholine, which has been shown to alleviate some of the symptoms of Alzheimer's disease. However, this increased level of acetylcholine is offset by increased inhibition of post-synaptic M_1 receptors, so many analogues of himbicine have been produced to try to reverse this selectivity and increase potency. As a result, three total syntheses of himbicine have been reported to date, and are outlined in the following section.

1.2 Strategies and methods for the synthesis of himbacine and related compounds

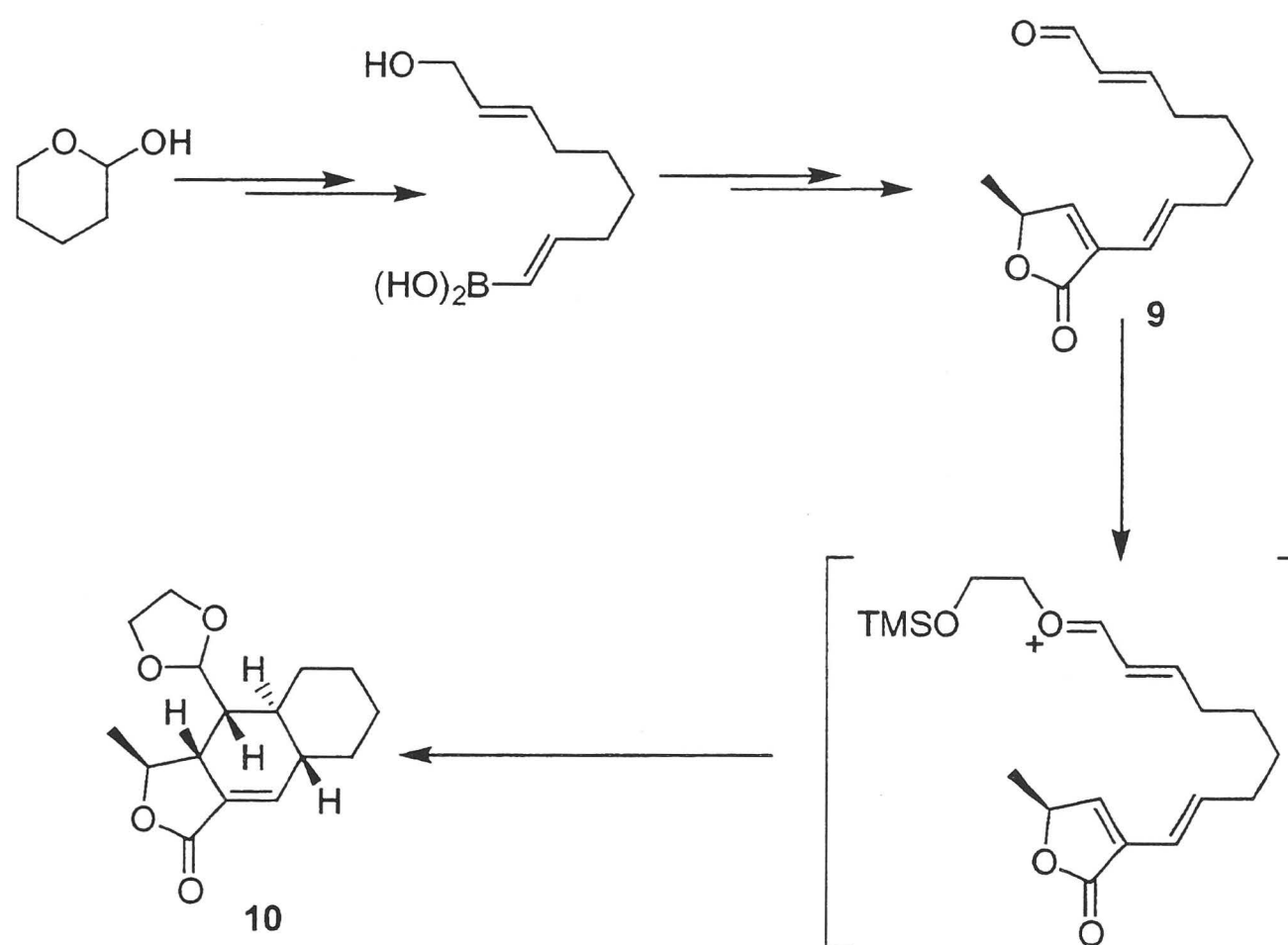
With a significant number of total syntheses of himbacine (1) being reported, most efforts are directed toward short convergent syntheses, with the ability to attach a number of different synthetic building blocks to an advanced intermediate so as to generate libraries of analogues for biological testing. As a result, the more common approaches utilise a Diels-Alder reaction for the construction of the tricyclic ring system followed by attachment of the piperidine ring system, or variations thereof.

Early work on the synthesis of himbacine and related alkaloids includes that of Baldwin *et al.* on a biomimetic approach to himgravine.⁷ He postulated that the iminium ion 8 is formed from the intramolecular condensation of a keto-amine precursor, and that this intermediate then undergoes a Diels-Alder cyclisation followed by reduction to give himgravine (3) (Scheme 1.1). To test his hypothesis, he constructed ene-diene 9 and generated an oxonium cation using Noyori acetalisation conditions at -78°C . Upon warming to -20°C , the cyclisation occurred over 2 hours to give the tricyclic material 10 in 53 % yield as a 40:1 mixture of diastereoisomers (Scheme 1.2).

Scheme 1.1



Scheme 1.2

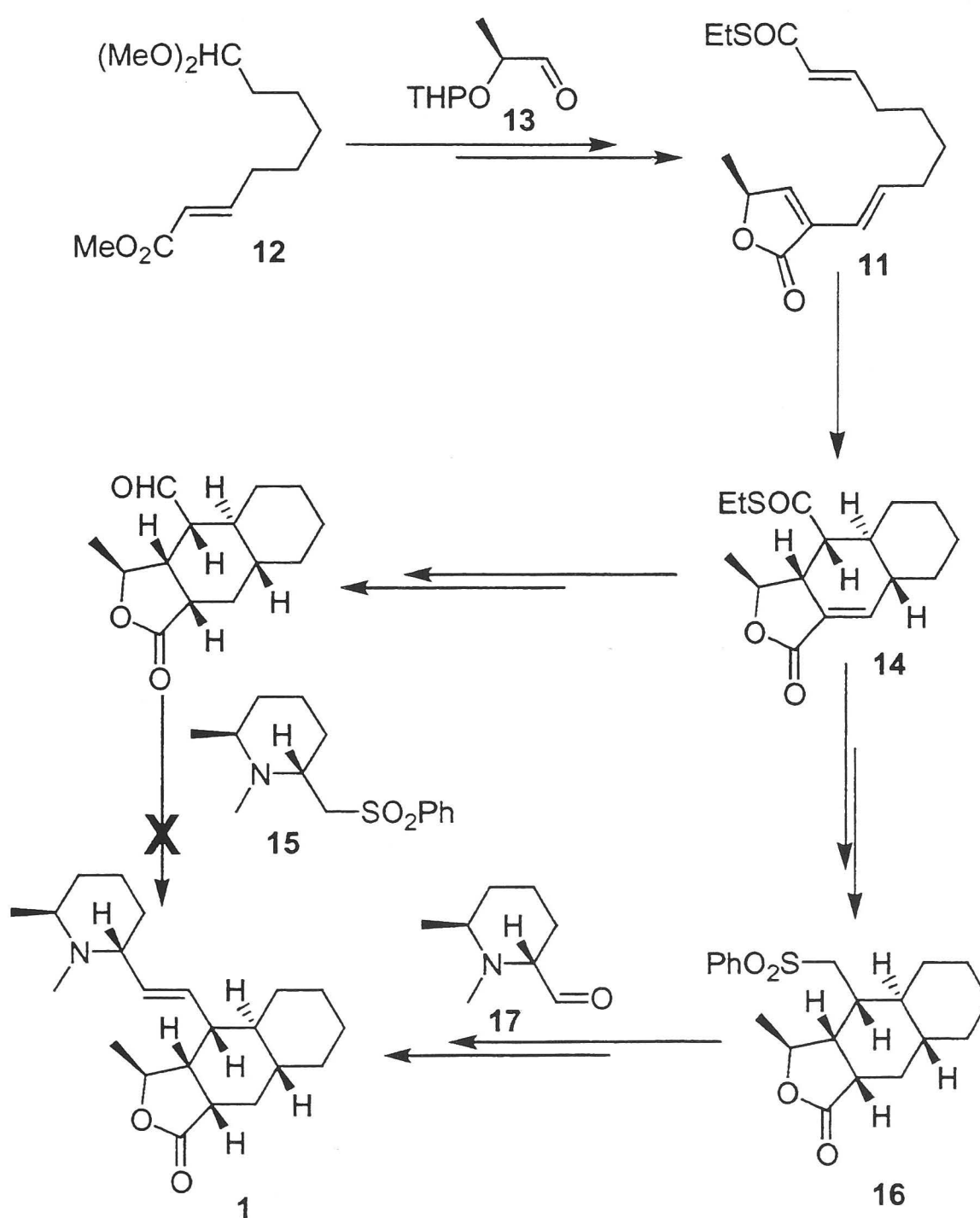


In a study published in the same year as Baldwin's work, Hart *et al.* used the same Diels-Alder disconnection in the first reported total synthesis of (+)-himbacine (1) and (+)-himbeline (2) (Scheme 1.3).⁸ The triene 11 was built from intermediate 12 by reaction with the enantiopure aldehyde 13. This triene underwent an intramolecular Diels-Alder reaction in the presence of diethylaluminum chloride on silica gel to give a 70% yield of a 20:1 mixture of *endo* isomer 14 with its *exo* isomer. The thioester was converted to the corresponding aldehyde in preparation for a Julia-Lithgoe coupling with sulfone 15, but this sterically hindered aldehyde failed to react. Swapping of the sulfone and aldehyde moieties, and subsequent reaction between 16 and 17 resulted in good yields of the desired adduct, which was further elaborated to (+)-himbacine 1 and (+)-himbeline 2.

The longest linear sequence in this synthesis involves 20 steps, and utilizes a highly selective Diels-Alder reaction. It is also reasonably flexible in that a variety of amino-aldehydes could be used in place of 17. However, the

sequence is long and requires two expensive enantiopure starting materials, which is a detraction for large scale synthesis.

Scheme 1.3

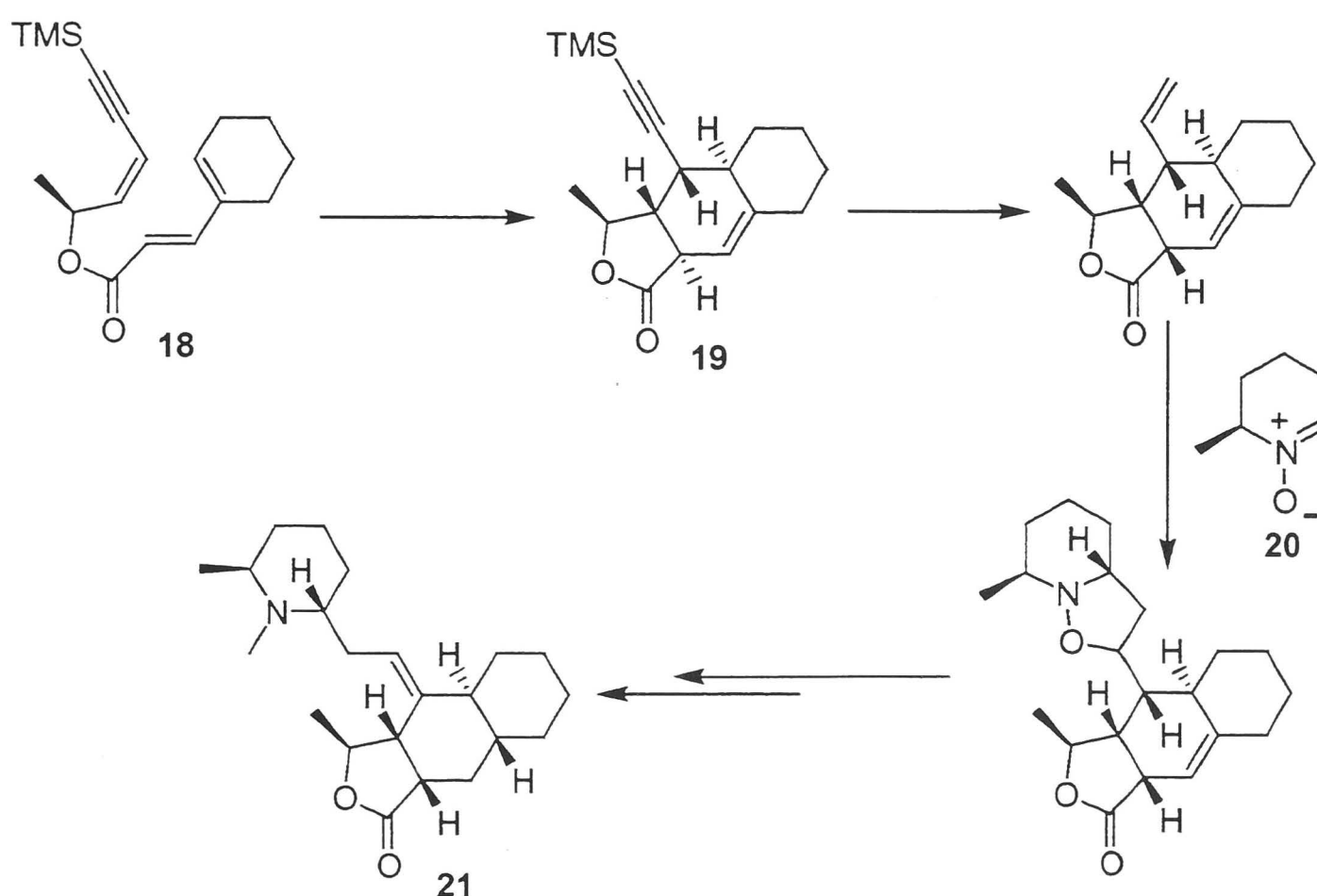


De Clercq *et al.* used a similar strategy to Hart *et al.* in their attempt for a total synthesis of (+)-himbacine (1), but their results were inferior to those of Hart as they were unable to obtain high selectivity in the Diels-Alder reaction and some steps were low yielding.⁹

Chackalamannil *et al.* developed a different approach to the Diels-Alder reaction, as outlined in Schemes 1.4 and 1.5.¹⁰ They generated the enantiopure triene 18, which underwent a smooth Diels-Alder cyclisation to

give the *trans* lactone **19**. The stereochemistry was not correct at the position α to the lactone carbonyl function, but this could be easily corrected by treatment with DBU. Reduction of the silylalkyne moiety to the alkene set the stage for an elegant attachment of the piperidine ring by a [2+3] cycloaddition with nitron **20**. Unfortunately, this approach was not successful, as elimination of the oxygen functionality to install the *trans* double bond found in the natural product failed to produce any of the desired material. Instead, isohimbacine **21** was the only product isolated.

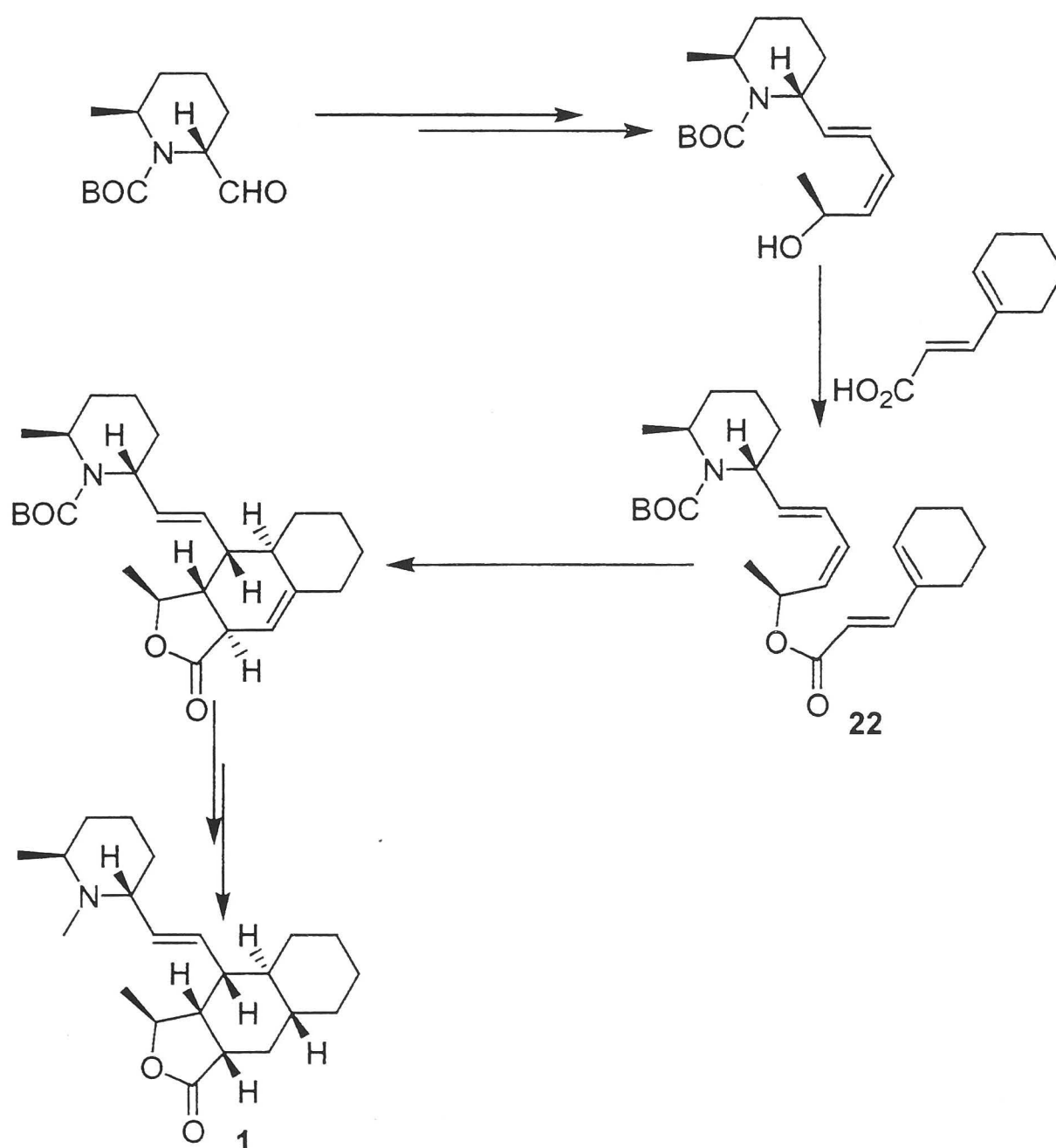
Scheme 1.4



In Chackalamannil's second generation approach (Scheme 1.5), he avoided the problems encountered previously by installing the piperidine ring at the start of the synthesis to give Diels-Alder precursor **22**. This cyclised to give the *trans* lactone which was isomerised to the *cis* compound, as for the previous synthesis. A regioselective reduction, followed by methylation, then gave (+)-himbacine **1** in 12 linear steps and 10% overall yield.

This work was further developed to generate libraries of himbacine analogues, a number of which showed reversed selectivity, compared to himbacine, for the M_1 versus the M_2 acetylcholine receptor.¹¹

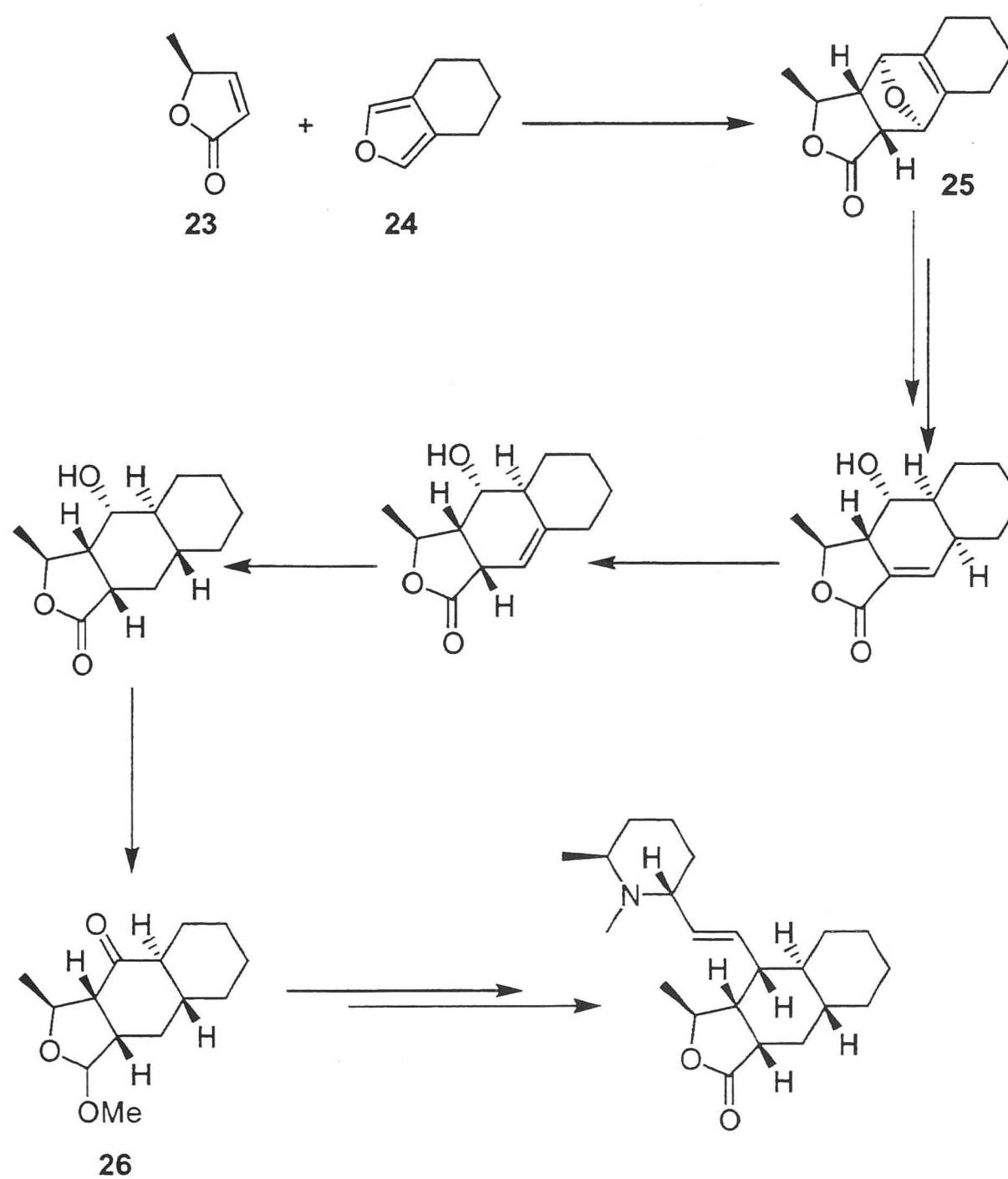
Scheme 1.5



Terashima *et al.* developed a synthesis that differed from the previous approaches by using an intermolecular Diels-Alder reaction, as this process can be readily modified to generate analogues within the tricyclic ring system of himbacine (Scheme 1.6).¹² The Diels-Alder reaction between enantiopure lactone **23** and furan **24** generated the oxo bridged compound **25** as the sole product in good yield. Reduction of the double bond and opening of the oxo bridge then allowed correction of the stereochemistry at the decalin ring junction. The synthesis was completed by homologation of

the ketone function in compound **26** followed by use of the Julia-Lithgoe sulfone coupling procedure employed by Hart to give (+)-himbacine in a total of 18 steps.

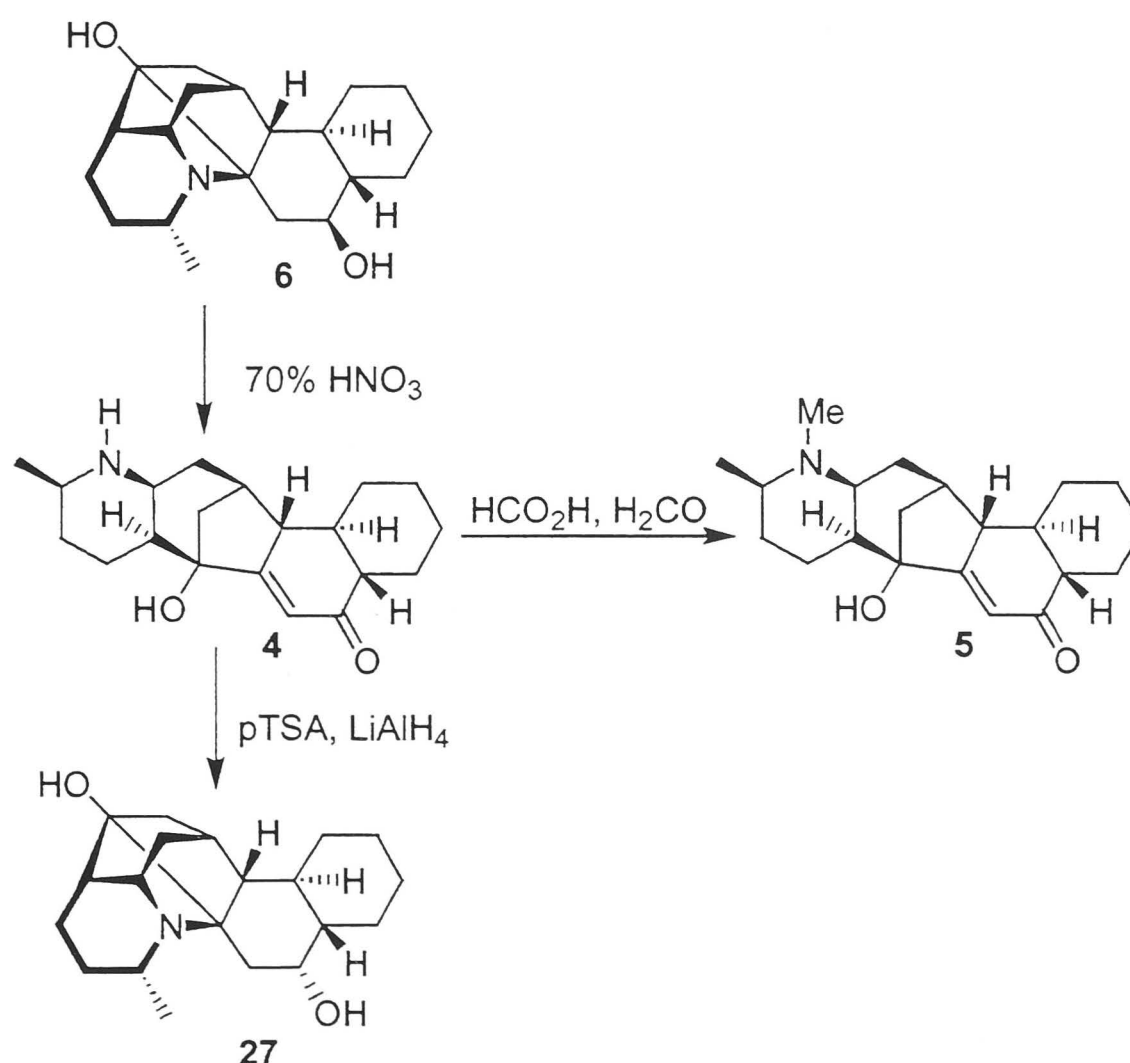
Scheme 1.6



1.3 Partial synthesis of himbadine, alkaloid GB 13 and 5-*epi*-himgaline

The structures of the bridged group of alkaloids were deduced in the 1960's by extensive degradation, spectroscopic studies and partial synthesis. The structure of himbosine (7a) was determined by X-ray crystallography and served as a reference point for the assignment of the structures of the remaining hexacyclic ester alkaloids 7b-o. This work has been thoroughly reviewed¹³ but the chemistry reported for himbadine, alkaloid GB 13 and himgaline is highly relevant to our work, and is summarised below.

Scheme 1.7

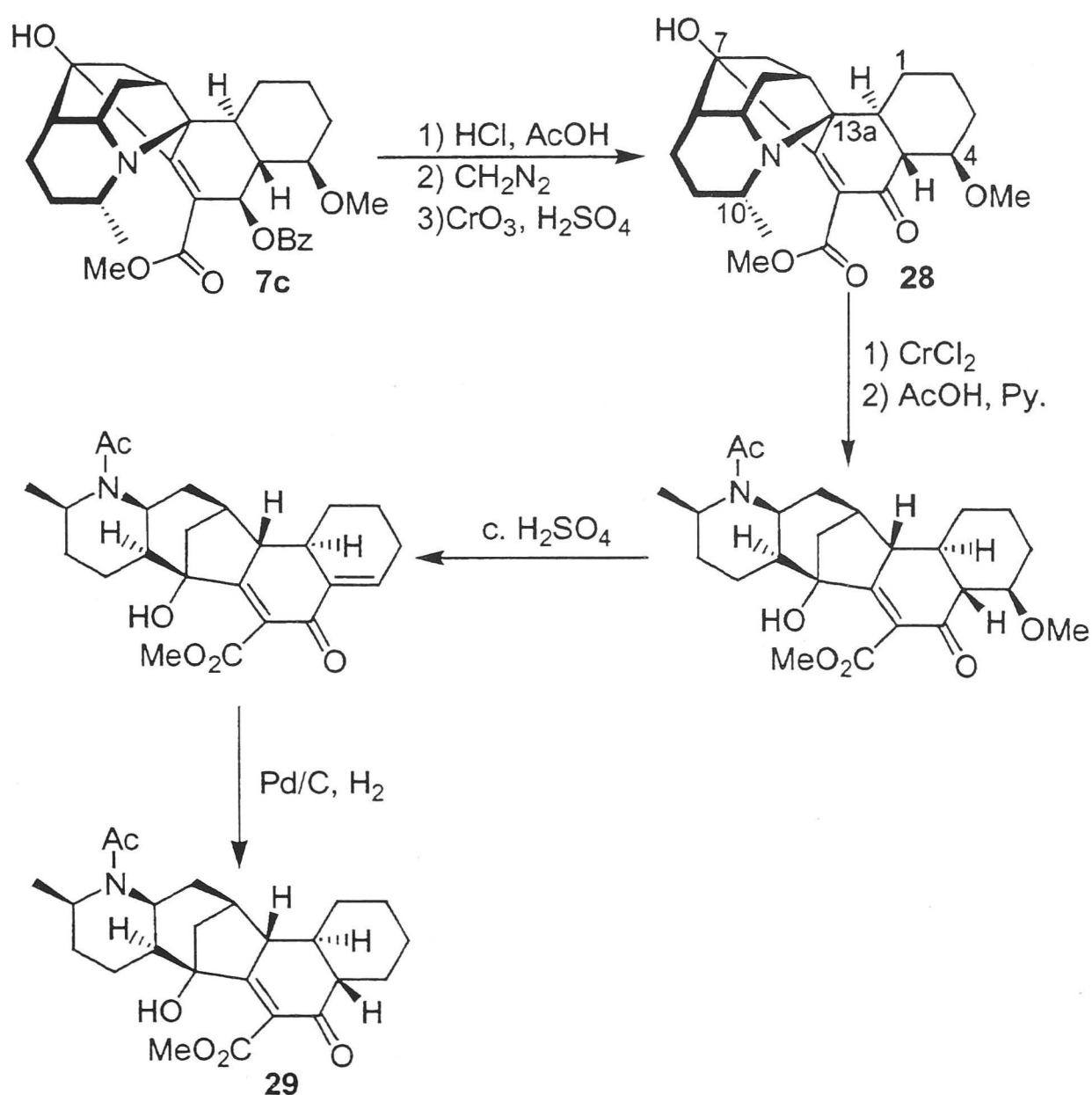


The three bases himbadine (5), alkaloid GB 13 (4) and himgaline (6) are closely related and can be interconverted (Scheme 1.7). Alkaloid GB 13 (4) was found to be *N*-demethyl himbadine and could be converted to

himbaine (5) by *N*-methylation with formic acid and formaldehyde. Also, himbaine could be converted to alkaloid GB 13 by brief treatment with 70% nitric acid, while alkaloid GB 13 could be converted to 5-*epi*-himbaine 27 by hydrogenation in the presence of acid or treatment with *p*-toluenesulfonic acid followed by lithium aluminum hydride.

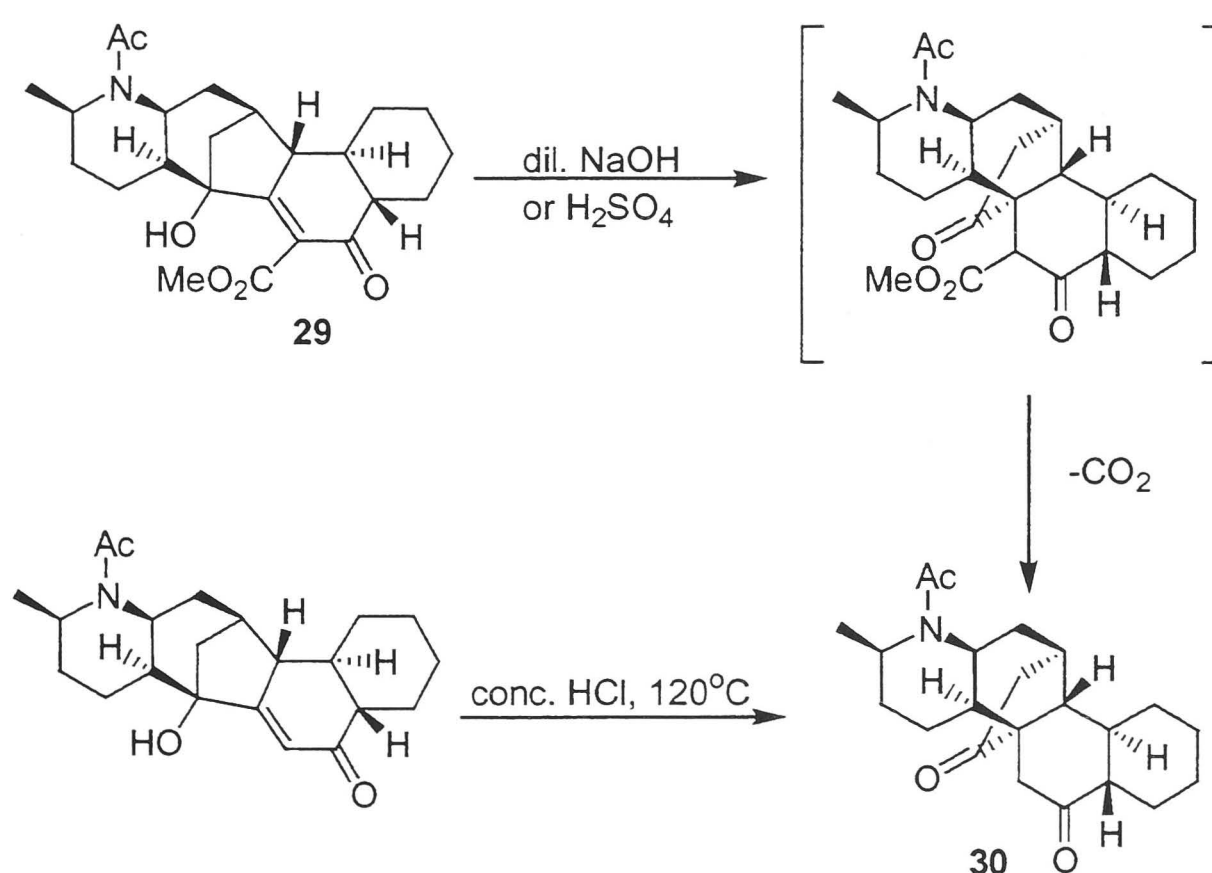
Alkaloid GB 13 was also partially synthesized from the 3-deoxy ester alkaloid himandrine (7c). The first attempt at the transformation is illustrated in Scheme 1.8. De-esterification, followed by oxidation with Jones' reagent gave enone 28. The heterocyclic cage was reductively cleaved at C13a with chromous chloride and the secondary amine function thus liberated was protected as its acetamide. Elimination of the C4 methoxy substituent followed by hydrogenation of the resulting alkene then gave ester 29.

Scheme 1.8



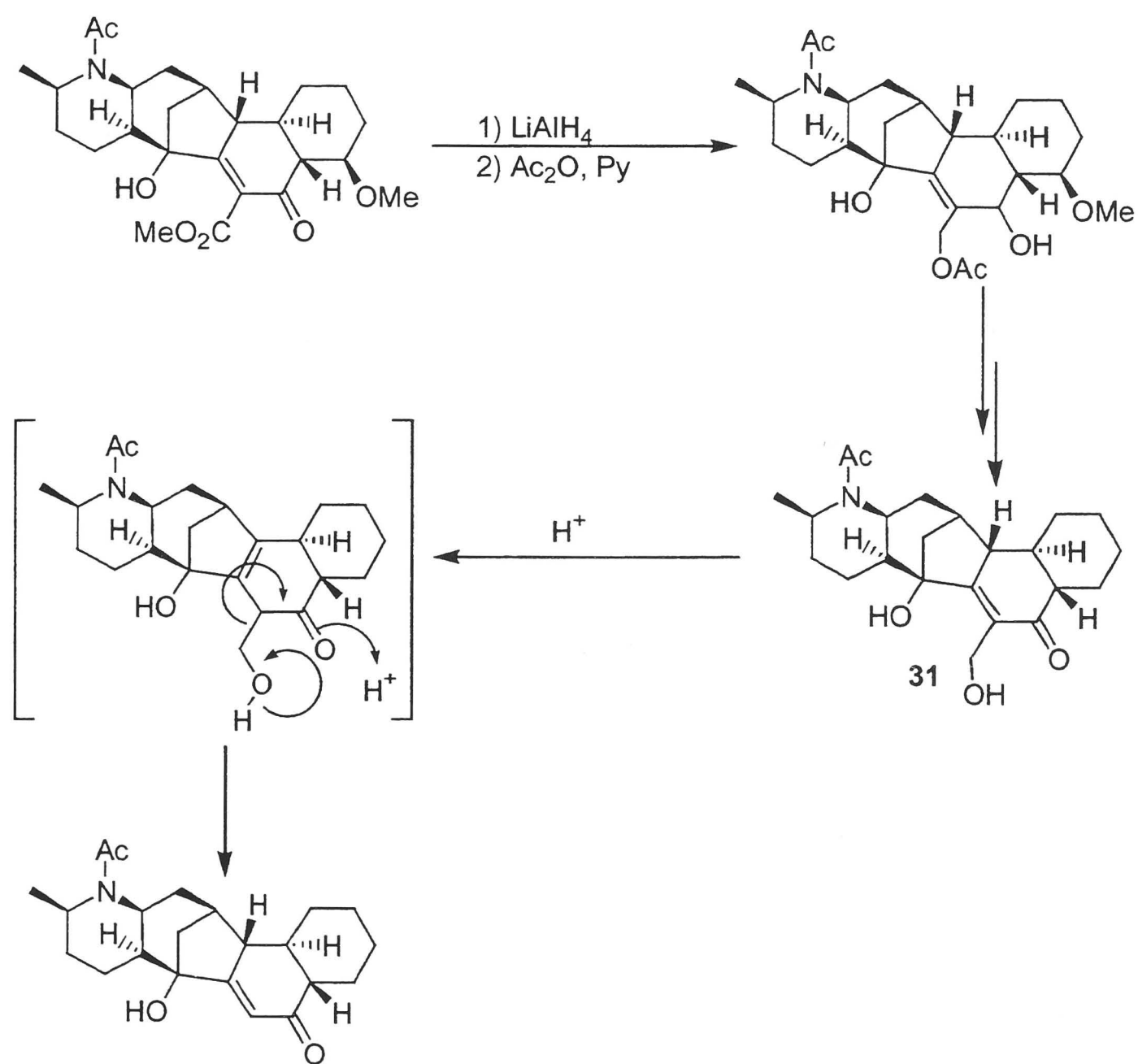
Unfortunately, attempts to hydrolyse and decarboxylate this material failed to generate *N*-acetyl GB 13. Instead, the carbon skeleton rearranged to give *N*-acetyl *iso*-GB 13 (**30**) (Scheme 1.9). It had been reported that this is a facile and common rearrangement when dealing with this bridged family of alkaloids, and indeed, it was found that *N*-acetyl GB 13 could also be rearranged to *N*-acetyl *iso*-GB 13 by treatment with hot acid.

Scheme 1.9



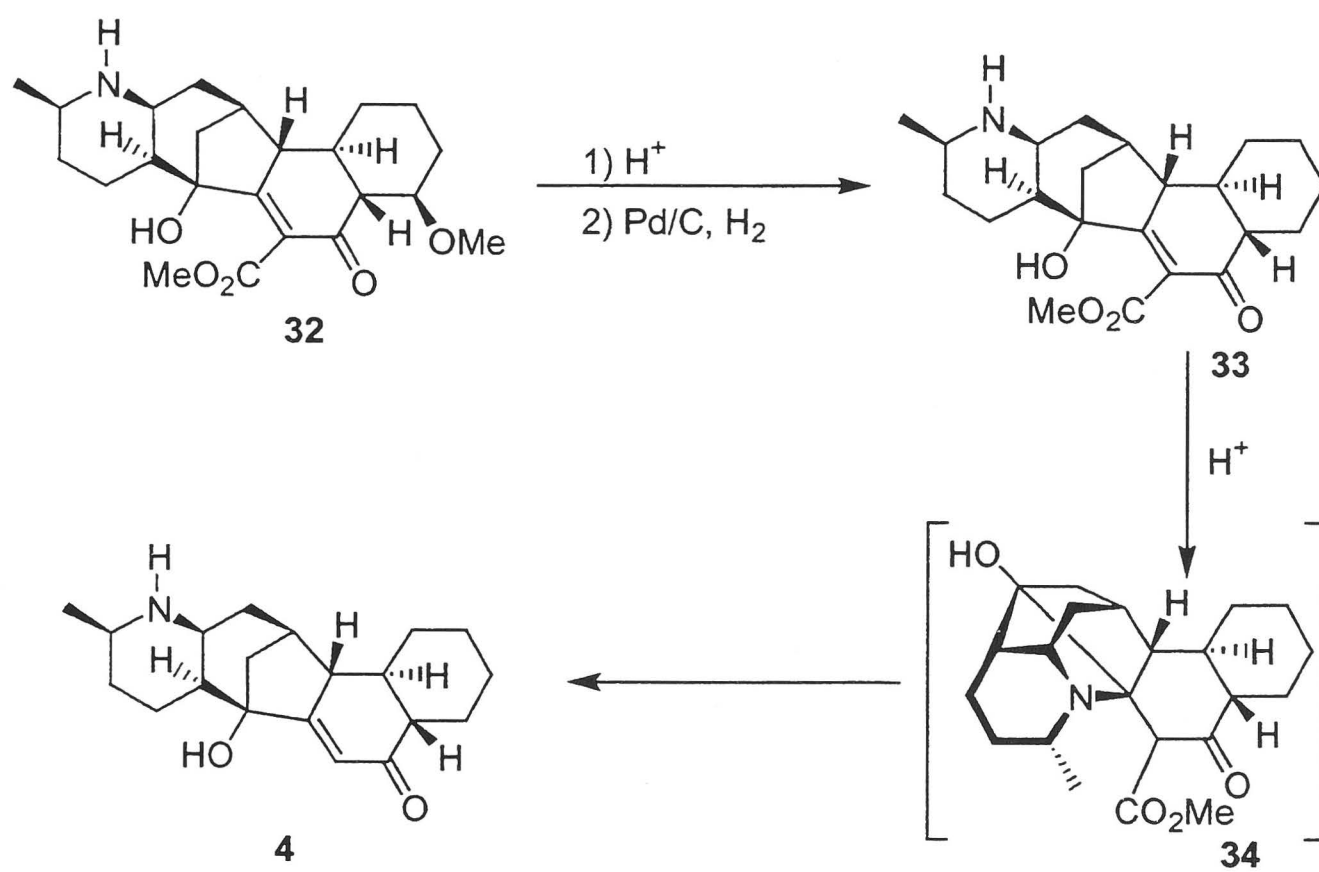
To help prevent this rearrangement, the ester was reduced to the corresponding alcohol and protected as its acetate in the hope that the migratory pathway would now be less favoured due to the reduced polarisation of the double bond. The compound was then treated as for Scheme 1.8 to give the allylic alcohol **31**. Treatment of this compound under basic conditions resulted in only starting material and *N*-acetyl *iso*-GB 13 being isolated, although it did undergo deformylation upon treatment with dilute acid to give *N*-acetyl GB 13 in low yield (Scheme 1.10).

Scheme 1.10



It had been noted that the olefinic proton of GB 13 slowly disappeared on standing with acid. This process was assumed to be due to acid catalysed intramolecular Michael addition of the amine function to the enone moiety. This observation was then exploited in the removal of the methoxycarbonyl group. Thus, treatment of secondary amine 32 with dilute acid, followed by hydrogenation gave amine 33, which underwent complete decarboxylation *via* intermediate 34 to give alkaloid GB 13 4 in excellent yield (Scheme 1.11).

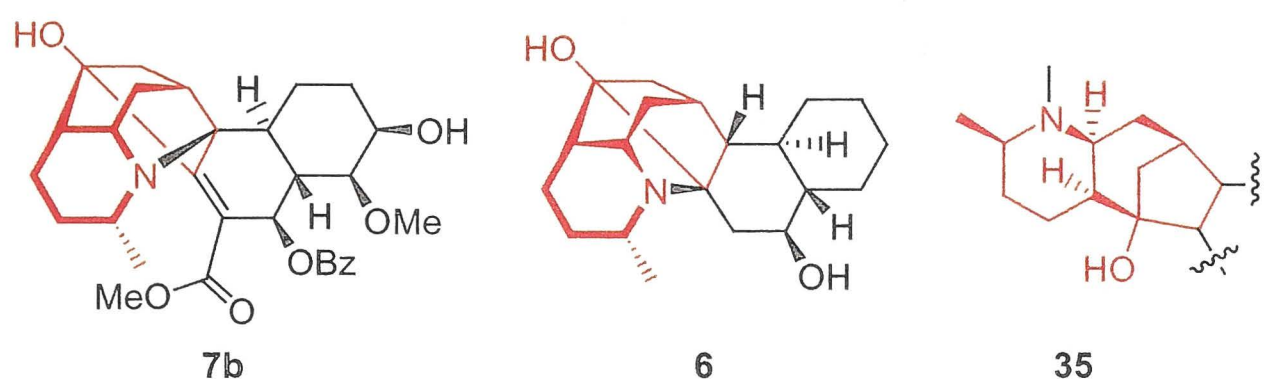
Scheme 1.11



1.4 An approach to the synthesis of himbadine, himgaline and alkaloid GB 13

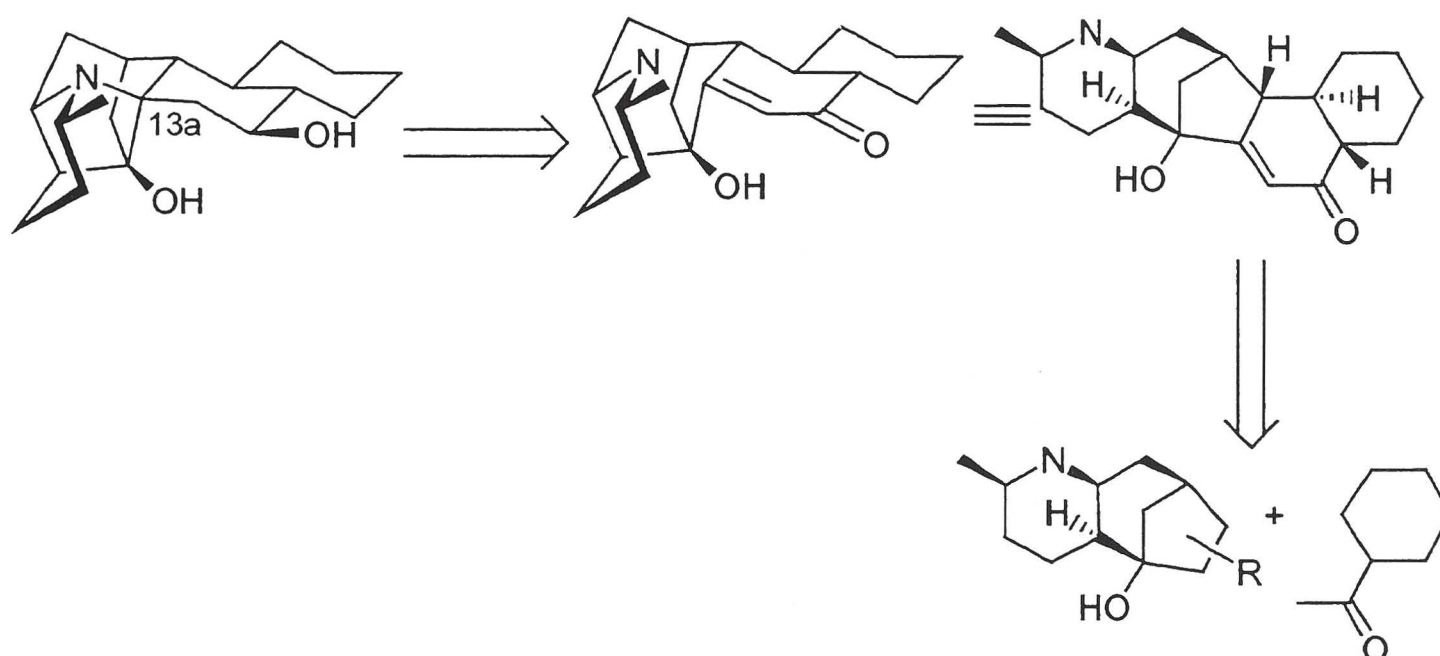
The central aim of this thesis is the development of an approach to the total synthesis of the "bridged" family of *Galbulimima* alkaloids, of which no total syntheses have yet been reported. We planned our approach to be general for both the hexacyclic ester alkaloids **7a-o** and the less highly functionalised hexacyclic and pentacyclic alkaloids GB 13 (**4**), himbadine (**5**) and himgaline (**6**). These aims appeared to be feasible since both groups of alkaloids contain the same tricyclic structure **35** outlined in red in Scheme 1.12. Our strategy was based on synthesising this tricyclic structure with functionality in place to then attach the decalin ring system.

Scheme 1.12



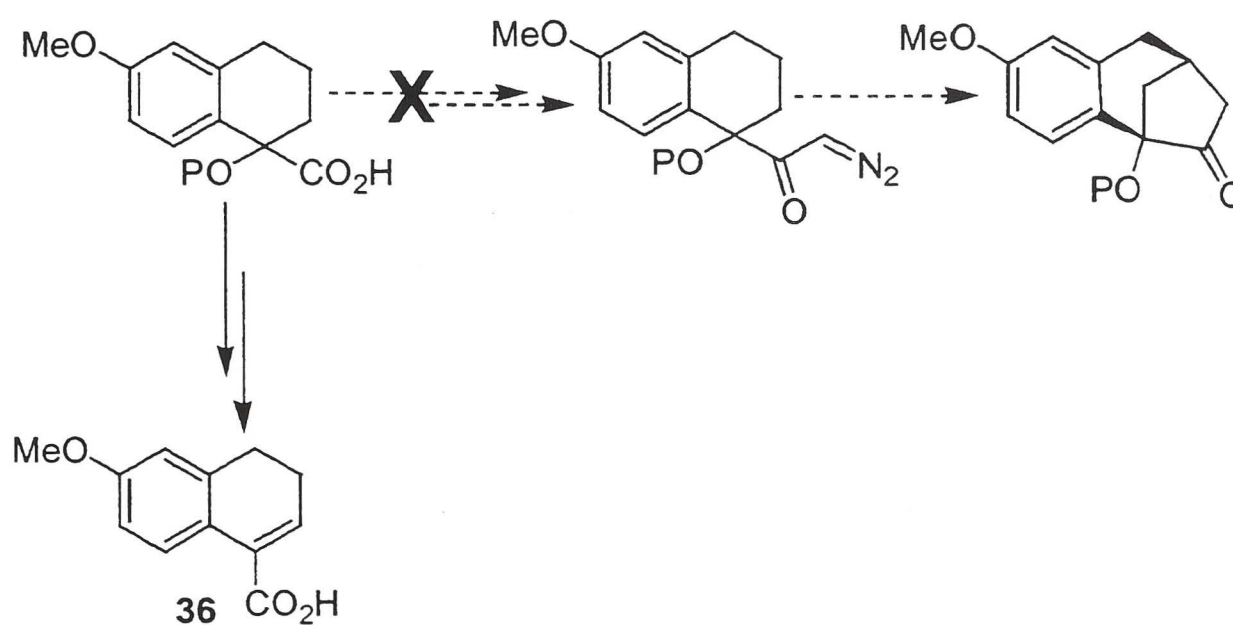
In our retrosynthetic analysis of himgaline, shown in Scheme 1.13, we first "disconnected" the nitrogen carbon bond at C13a to give an alkaloid GB 13 derivative, as the partial synthesis work carried out previously indicated that the synthetic equivalent of this disconnection will be straightforward. Cleavage of the decalin ring system then leads to a substituted cyclohexene and the tricyclic moiety.

Scheme 1.13



Mander and Wells had previously attempted to synthesise a suitably functionalised tricyclic structure using diazo insertion methodology as outlined in Schemes 1.14 and 1.15.¹⁴ Unfortunately, the precursors were unstable and often dehydrated to give dihydronaphthalene derivatives such as compound 36.

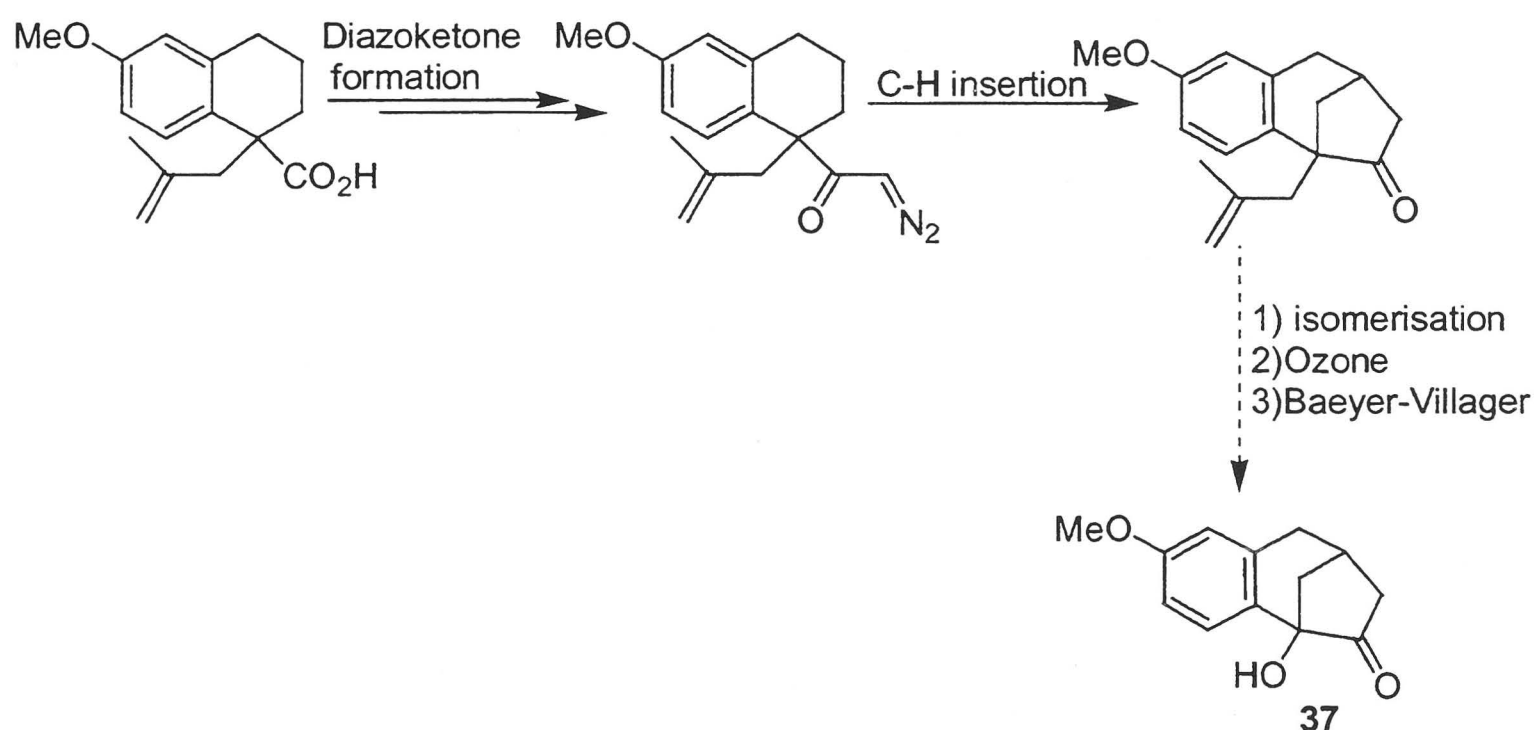
Scheme 1.14



Replacing the labile oxygen functionality at the benzylic position with various alkyl chains did result in suitable C-H insertion precursors, and these could be cyclised to the bicyclic ring system in good yield.

Unfortunately, attempts to isomerise and oxidatively cleave the alkyl side chain, as outlined in Scheme 1.15, to give the desired bridgehead hydroxy compound **37**, failed.

Scheme 1.15



As a direct synthesis of the tricyclic moiety did not appear feasible we looked at alternative methods for its synthesis. Our attention was drawn to work reported earlier by Mander *et al.* on the total synthesis of gibberellins,¹⁵ that had given material that we thought could be readily converted to our target structure. They reported that compounds of type **38** could be cyclised to either bicyclononanes **39** or fluorenones **40**, depending on the R substituents and the conditions used.

As can be seen from Table 1.2, electron rich systems with groups in the 3 and/or 5 position will cyclise to the fluorenone in concentrated acid, while systems lacking both these attributes will cyclise to the [3.3.1]bicyclononane or not react at all, as in the case of the 4-methoxy compound. It was also found that the electron rich compounds could be cyclised to give the bicyclononane, if the reaction was carried out in dilute acid.

Scheme 1.16

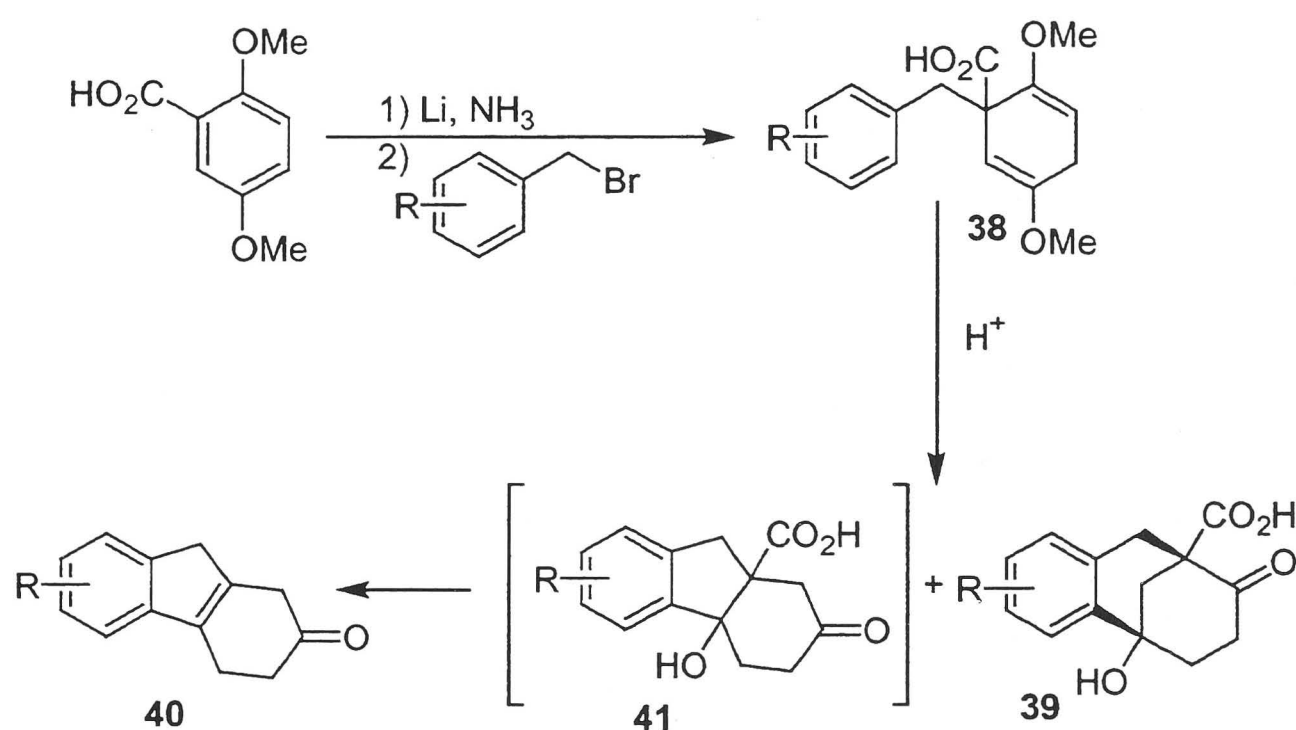


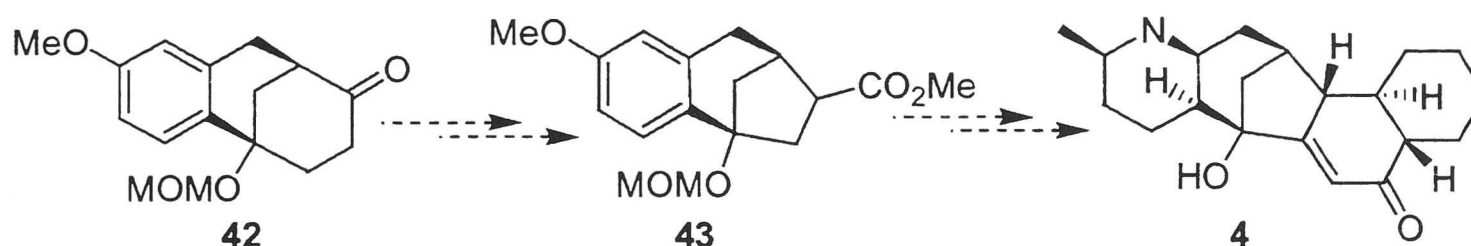
Table 1.2: The effects of varying substitution patterns on the acid catalysed cyclisation shown in Scheme 1.16

Compound	R substituents	Product
38a	3-OMe	40a
38b	3-OMe, 5-OMe	40b, 39b (in 1M HCl)
38c	2-CO ₂ Me, 3-OMe	40c
38d	4-OMe	No reaction
38e	H	39e
38f	2-Me	39f

These results were rationalised by assuming that the bicyclononane was produced first as the kinetic product. However, in strong acid this cyclisation is reversible and some of the fluorenone intermediate **41** could then form. This material can then decarboxylate and dehydrate in a non-reversible manner to give the fluorenone **40** as the thermodynamic product. It was hoped that the cyclisation process could be controlled to produce the novel 3-methoxy bicyclononane **42**, after which a ring contraction, such as a Wolff rearrangement of the α -diazoketone derivative, would give a suitable

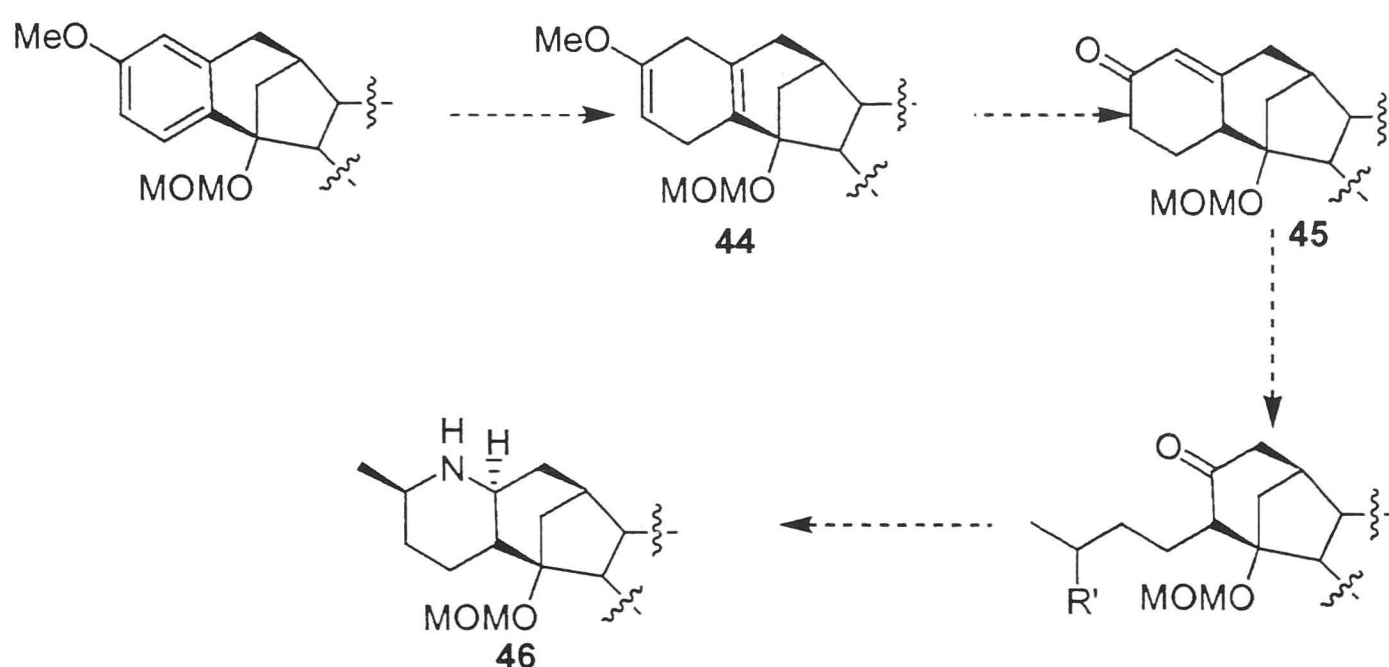
tricyclic, such as 43, that could then be elaborated to alkaloid GB 13 (4) (Scheme 1.17).

Scheme 1.17



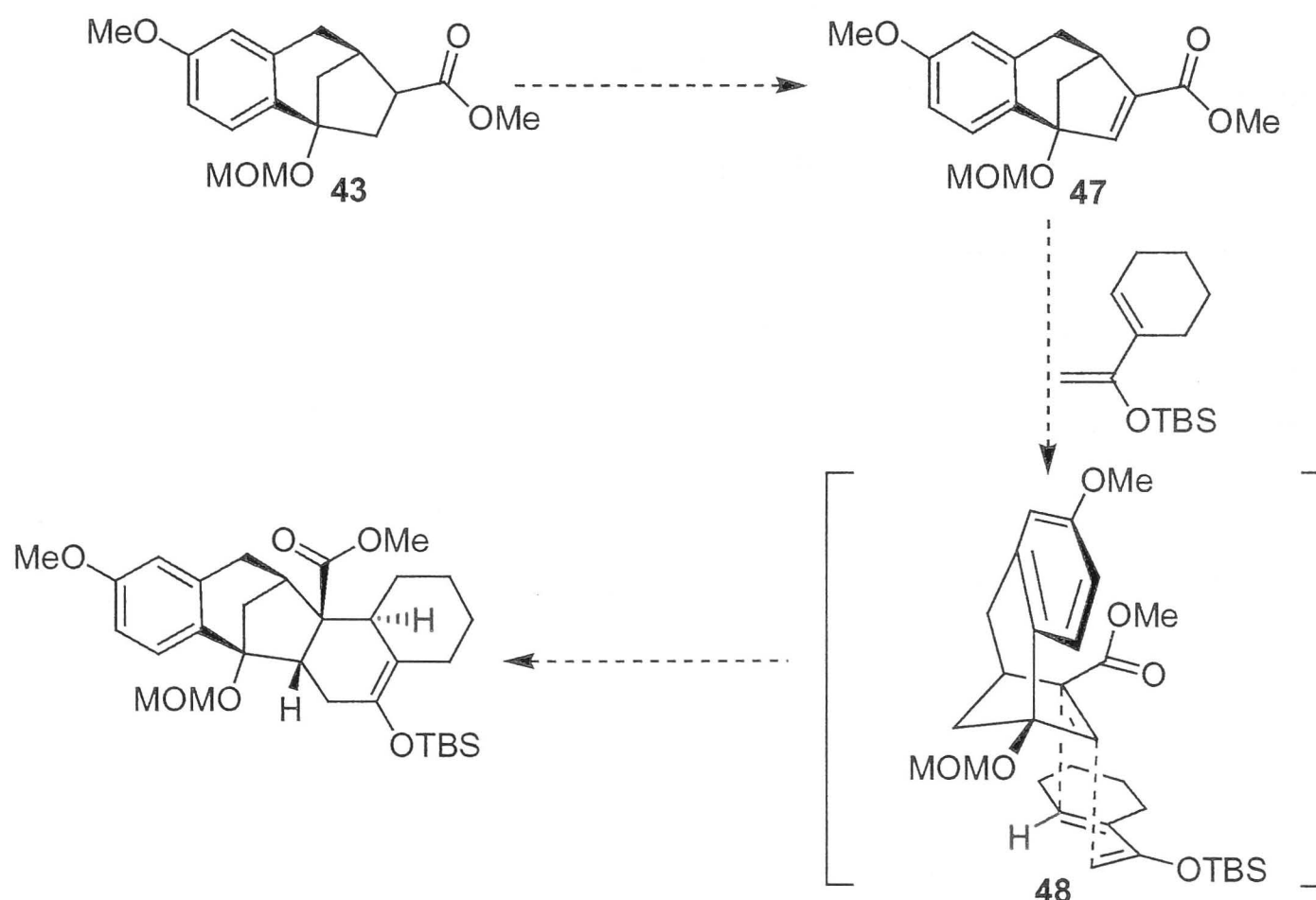
With this approach, it would be necessary to convert the benzenoid ring of the intermediate into the piperidine ring of the natural product. Birch reduction of the 3-methoxybenzene moiety is an important and synthetically useful reaction that is well established in the literature.¹⁶ It can be converted to a number of functional groups and yet it is also robust and can withstand many of the reaction conditions that prevail in the early stages of the synthesis. It was proposed that at a late stage in this synthesis the aromatic ring could be reduced and then converted to the enone 45. This intermediate could then be oxidatively cleaved using any one of a variety of methods to allow the subsequent introduction of ammonia, after which recyclisation would then give the desired piperidine ring of compound 46.

Scheme 1.18



Another consideration necessary for this synthetic route is the extruded carbon substituent from the ring contraction. It appeared to be impractical to incorporate it into the decalin ring system, so it was felt that a more viable route would be to convert the [3.2.1]bicyclooctane **43** to the dehydro compound **47** and then to attach the decalin rings using a Diels-Alder reaction. There are several advantages to this plan, but the most important is the expected diastereoselectivity in favour of the *endo* transition state **48** shown in Scheme 1.19, which is essential to give the correct relative stereochemistry for the decalin ring junction. Hydrolysis of the silyl enol ether could then be expected to give the *trans* ring junction found in the natural products.

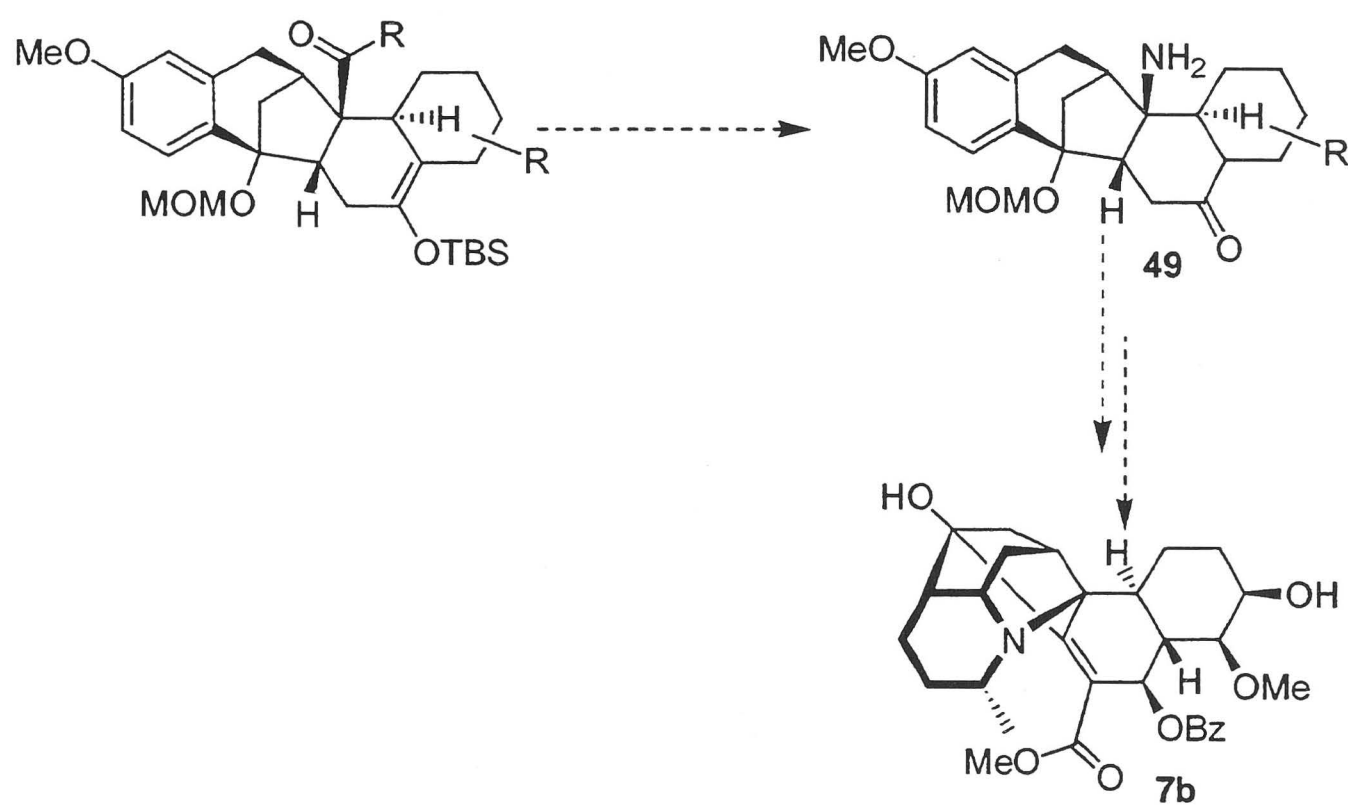
Scheme 1.19



In addition, the extruded carbon could provide an opportunity for the introduction of nitrogen into the himandridine family of ester alkaloids **7a-o** by means of a Curtius or Hoffmann rearrangement to give compounds of the type **49** (Scheme 1.20). For the synthesis of alkaloid GB 13, however, the

extruded carbon could be removed by a deformylation or decarboxylation reaction. Taking into account these considerations, the synthetic plan outlined in Scheme 1.21 was pursued.

Scheme 1.20



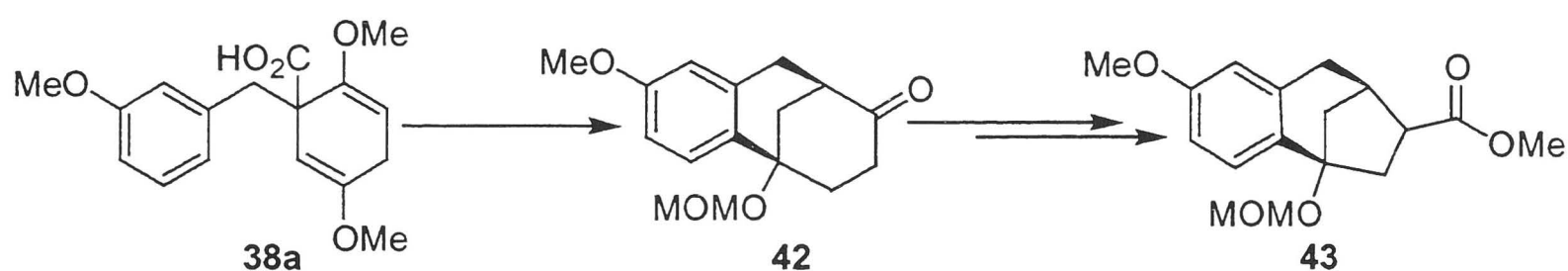
Chapter 2

Synthesis of the carbon skeleton

2.1 The synthesis of a suitable [3.3.1]bicyclononane derivative

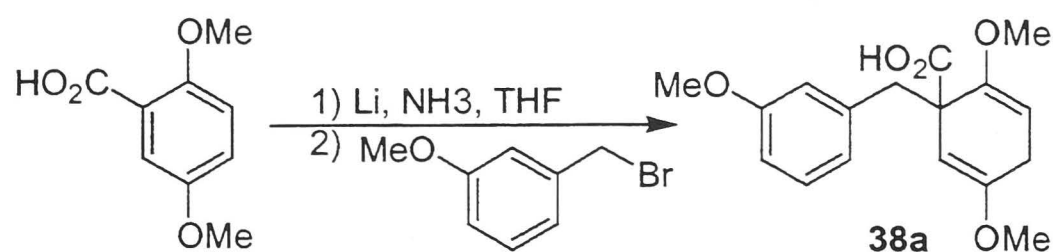
In this chapter, an approach to the target intermediate [3.2.1]bicyclooctane will be discussed. As mentioned in the introduction, acid catalysed cyclisation of readily synthesised 2-benzyl-1,3-dienol ethers can lead to either fluorenones or [3.3.1]bicyclononanes. The novel 3-methoxy bicyclononane **42** was required for this synthesis, since a ring contraction should then afford the target [3.2.1]bicyclooctane **43** (Scheme 2.1).

Scheme 2.1



The 2-(3-methoxybenzyl)-1,3-dienol ether **38a** could be synthesized in excellent yield (80 %) and on a large scale (45 g) by following the literature procedure of Mander and Hook (Scheme 2.2).¹⁵ This white, crystalline material decomposes at room temperature, but could be stored at -18°C. This material was used without purification in the subsequent cyclisation step.

Scheme 2.2



A variety of acid concentrations for the cyclisation were tried (Scheme 2.3), and the results are tabulated in Table 2.1. At low acid concentrations, mainly

the uncyclised product **50** was isolated, but at moderate acid concentrations, [3.3.1]bicyclononanes could be obtained. However, below a concentration of about 50% sulfuric acid the decarboxylated material **51** was also formed, presumably from cyclisation of the decarboxylated material **50**. In a separate experiment, it was shown that the diketone **50** would cyclise in 45% sulfuric acid to give a mixture of starting material and the decarboxylated [3.3.1]bicyclononane **51**. At 60% sulfuric acid, only the carboxylic acid **39a** was isolated, although trace amounts of other products could be observed by ^1H -NMR spectroscopy. At acid concentrations exceeding 85% sulfuric acid, the only product isolated was the fluorenone **40a**.

Scheme 2.3

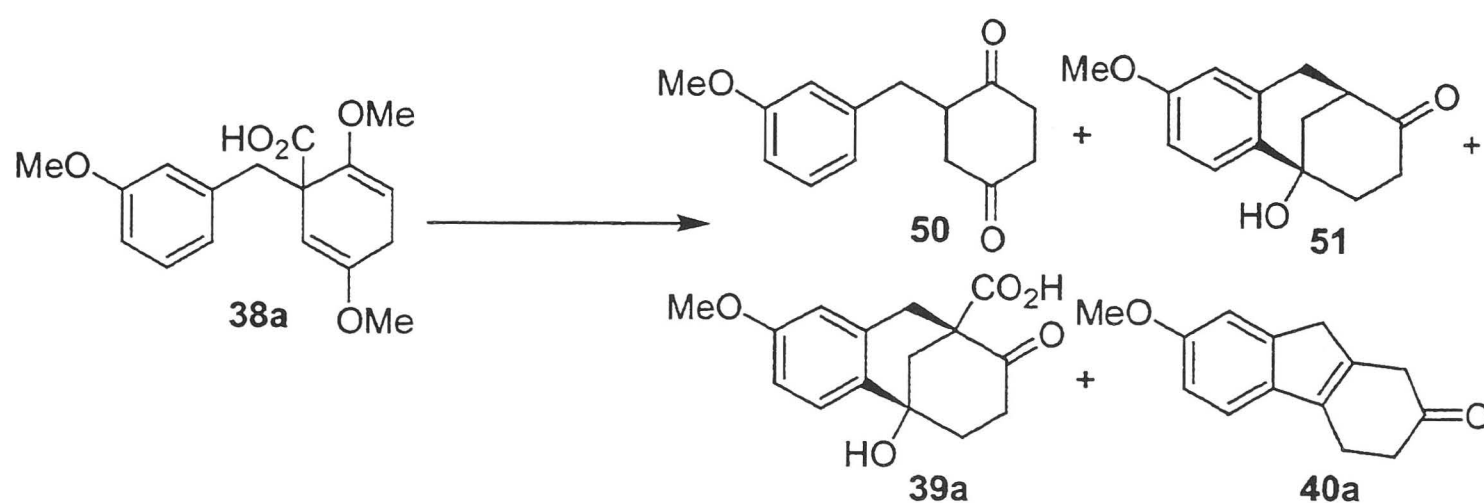


Table 2.1: Product distribution in the acid catalysed cyclisation of **38a**

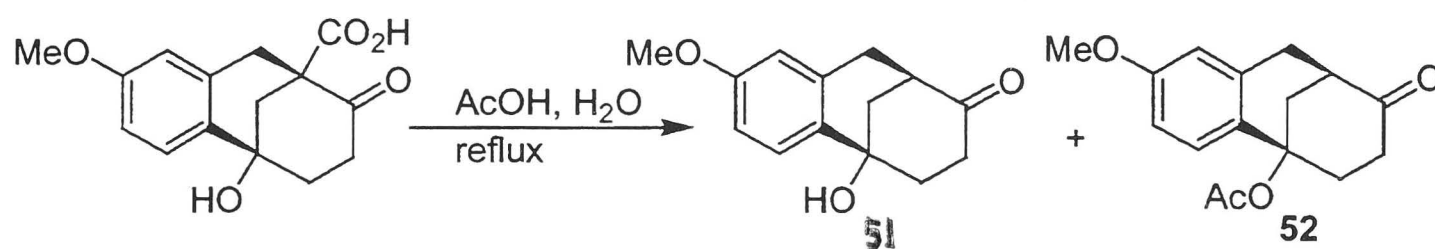
Concentration of H_2SO_4 (v/v)	Product ratio (by ^1H -NMR)			
	50	51	39a	40a
30%	1:	trace:	trace:	0
45%	0:	1:	1:	0
60%	0:	trace:	1:	trace
85%	0:	0:	0:	1

While high yields of the desired decarboxylated material **51** could be obtained by a judicious choice of reaction conditions, this material could

only be obtained as an impure brown oil that resulted in practical problems with purification on a large scale. This outcome was in sharp contrast to the formation of the carboxylic acid **39a**, which is a white crystalline compound and which was readily purified by recrystallisation from ethyl acetate/petroleum spirit.

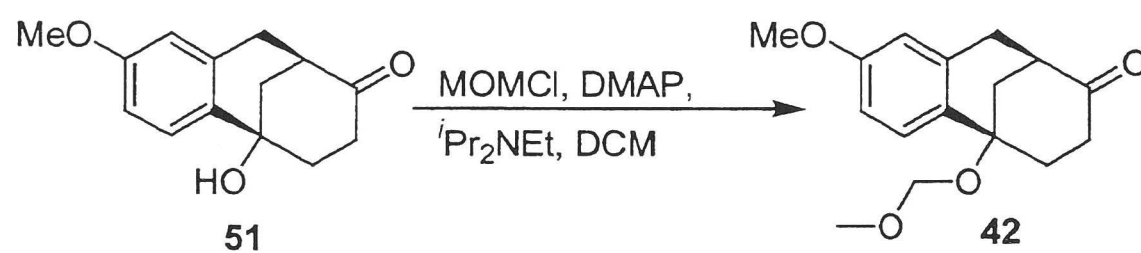
It was found that on a large scale it was most practical to use 60% sulfuric acid for the cyclisation to give the carboxylic acid **39a**. This material could then be decarboxylated subsequently in good yield by heating in wet acetic acid at reflux for 16 hours (Scheme 2.4). Omission of the water in this reaction resulted in a poor conversion of the starting material to the product, and the isolation of a significant amount of the acetate **52**.

Scheme 2.4



The free hydroxyl on the decarboxylated material **51** required protection, as it must be carried through many steps where it could undergo unwanted side reactions. The protecting group must be stable to most reaction conditions, while being of small steric demand due to the hindered environment it must eventually inhabit. The methoxymethyl ether group was chosen, as it is relatively robust, and stable to Birch reductive conditions. The methoxymethyl ether **42** could be formed in good yield by using standard conditions, consisting of DIPEA, catalytic DMAP and MOMCl in DCM (Scheme 2.5).¹⁷ This protected intermediate was then ready for the exploration of the ring contraction.

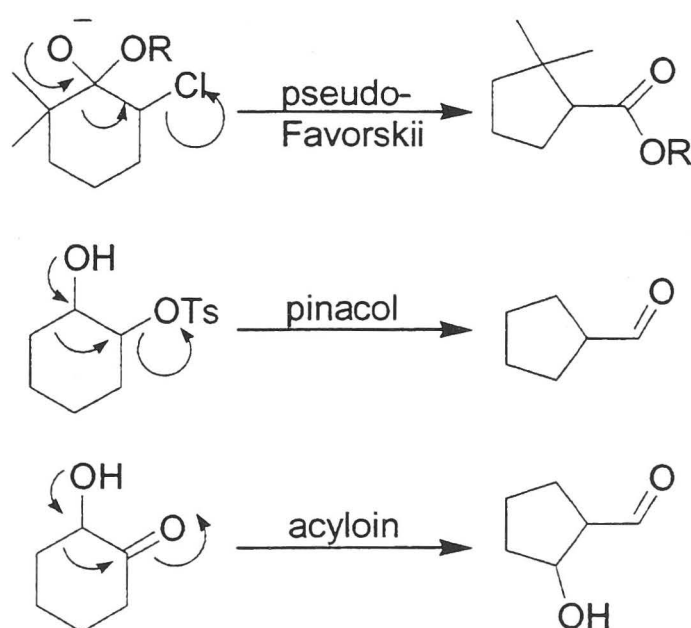
Scheme 2.5



2.2 The synthesis of [3.2.1]bicyclooctane derivatives

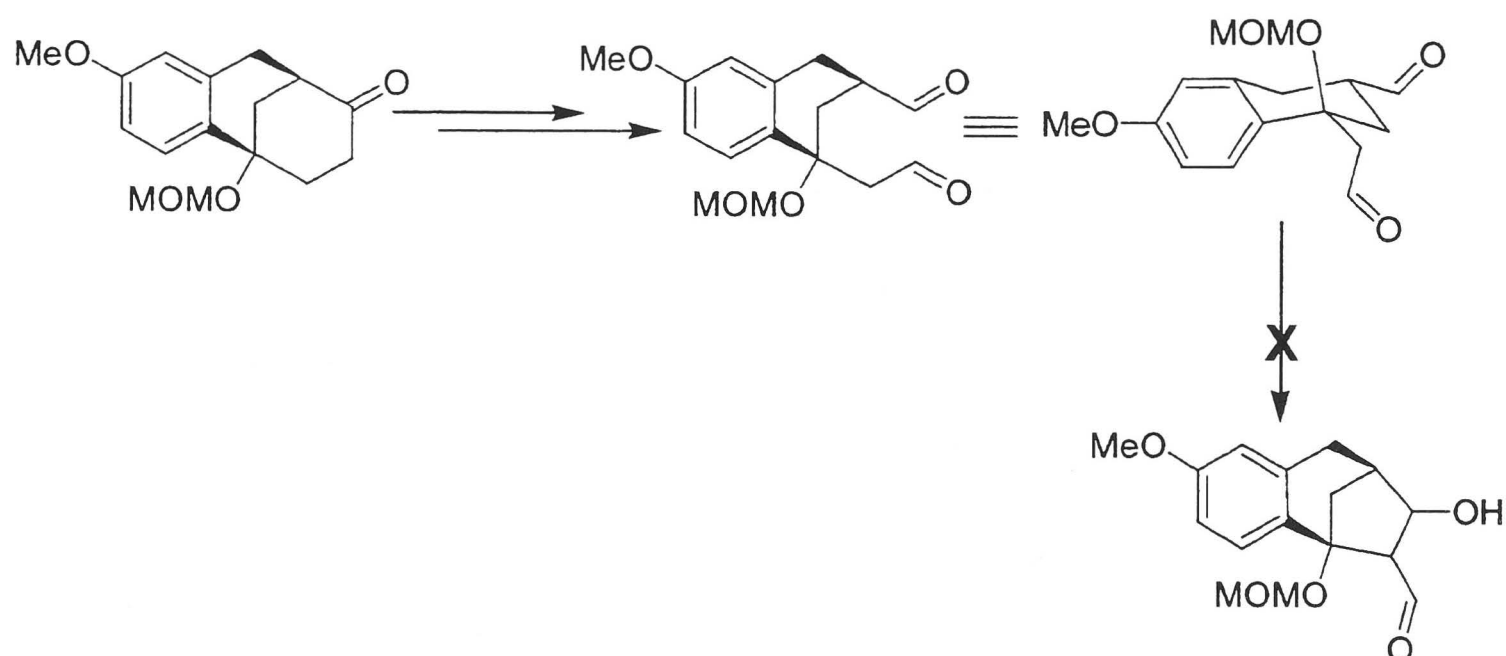
There have been many different methods developed for ring contractions such as the Favorskii,¹⁸ pinacol¹⁹ and acyloin²⁰ rearrangements, ring cleavage followed by an aldol reaction, and the Wolff rearrangement.²¹ The first three ring contraction methods are often problematic: e.g. attaining the correct stereochemistry for the desired orbital overlap, undesired rearrangements and the reversibility of the processes.

Scheme 2.6



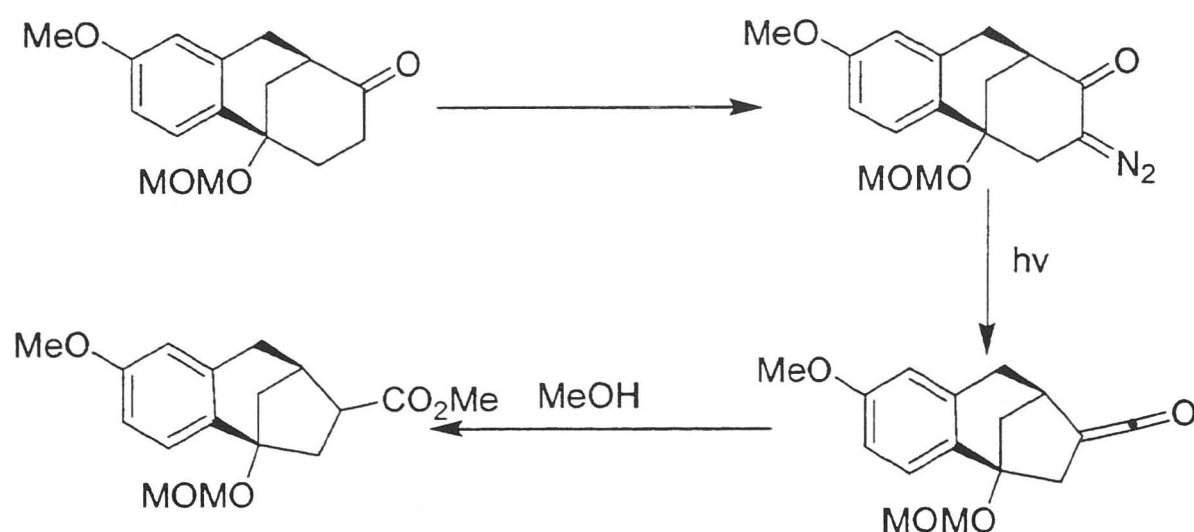
The use of a multistep procedure involving ring cleavage followed by an aldol reaction is even less suitable for this transformation, as the ring cleavage product would almost certainly take up the more stable diequatorial conformation, with the result that the desired intramolecular aldol reaction would not be favoured (Scheme 2.7).

Scheme 2.7



The Wolff ring contraction is less likely to suffer from these problems as the precursors are planar and the intermediates are formed irreversibly, without ring opening. The procedure involves forming an α -diazoketone, followed by photolysis in a nucleophilic solvent such as methanol (Scheme 2.8). The diazo ketone irreversibly loses nitrogen and rearranges to an intermediate ketene, which can then react with the solvent to give a carboxylic acid derivative.²¹ With these considerations in mind, it was decided that the Wolff ring contraction was the best option for this synthesis, so methods for the synthesis of α -diazoketones were explored.

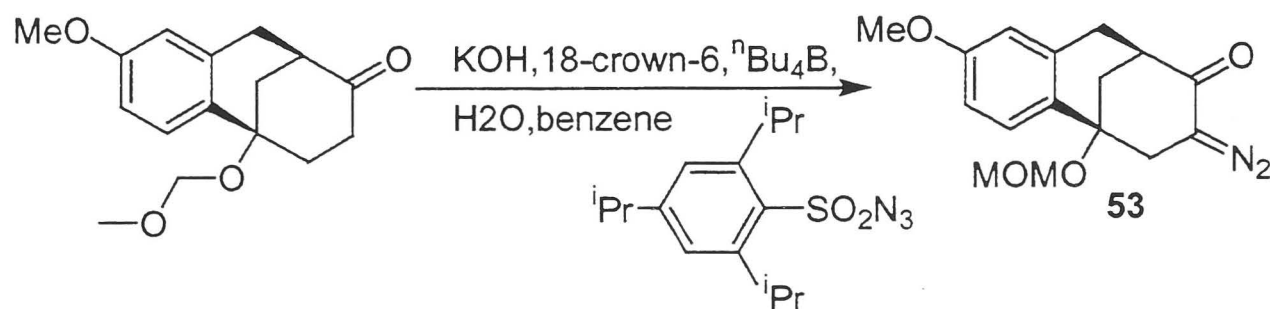
Scheme 2.8



While there are many methods available for the conversion of ketones to diazoketones in the literature,²² these reactions are often low yielding. The method that was investigated first was diazo group transfer from a sulfonyl azide²³ as this was the most promising, and most commonly used procedure. This methodology works well for 1,3-dicarbonyl systems such as β ketoesters, but for this procedure to work for simple ketones it often requires an activating group to be added prior to diazo transfer.

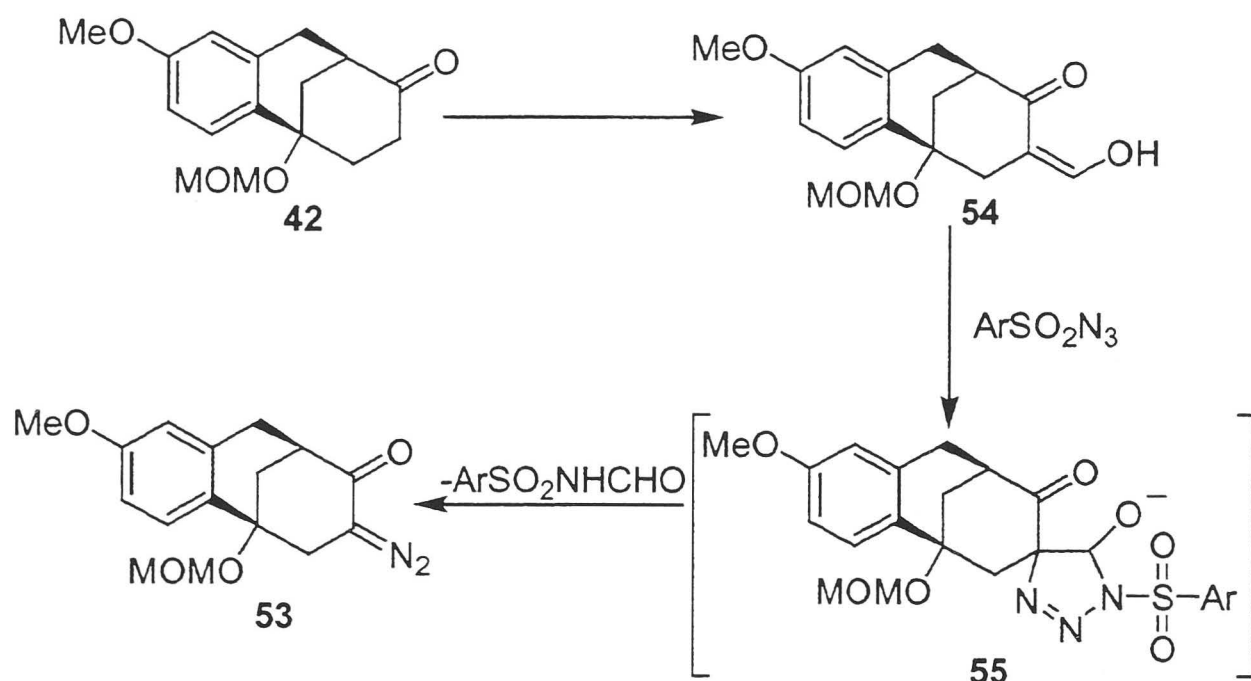
Nevertheless, the use of a "one pot" procedure using phase transfer conditions has been employed successfully on a range of simple cyclic ketones.²⁴ This seemed to be the most expeditious route to the required diazoketone **53**, but unfortunately the yields from this procedure were only 20-35% (Scheme 2.9).

Scheme 2.9



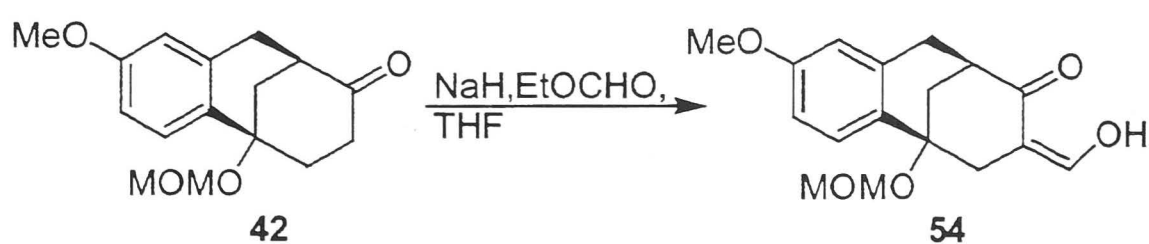
Since the "one pot" procedure was ineffective, the more commonly used two stage Regitz procedure was investigated instead. This method involved prior formation of α -hydroxymethylene-ketone **54** *via* a Claisen reaction, followed by a [3+2] cycloaddition to an aryl sulfonyl azide to give a triazoline intermediate **55**. This intermediate then decomposed to the diazoketone and the aryl sulfonyl formamide (Scheme 2.10).²³

Scheme 2.10



Treatment of ketone **42** with sodium hydride in THF, followed by the addition of ethyl formate, resulted in a high yield of the α -hydroxymethylene-ketone **54**. This material was unstable toward silica, so could not be purified, but the ^1H -NMR spectrum showed no sign of any other product. As expected, there was a peak at 8.58 ppm in the ^1H -NMR spectrum indicative of the proton on the hydroxymethylene group.

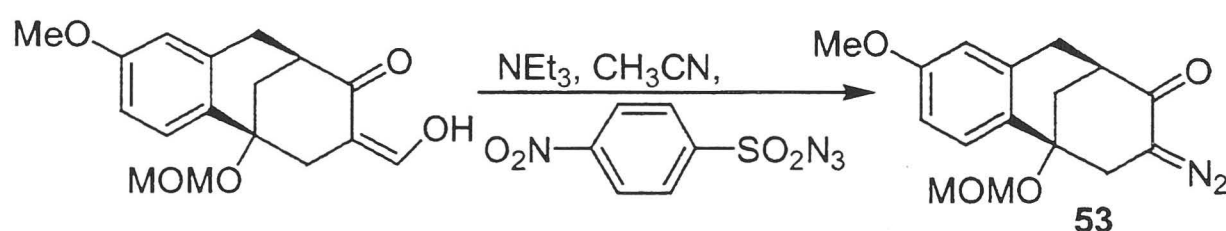
Scheme 2.11



This material was used without delay in the diazo transfer reaction. There are several choices of sulfonyl azide available for this reaction, of which tosyl azide is the most common. However, it is recognized that electron-withdrawing groups on the aromatic ring facilitate this reaction. *p*-Carboxy-benzenesulfonyl azide is often found to be superior,²⁵ but the cost is prohibitive on a large scale. A cheaper alternative is *p*-nitro-benzenesulfonyl azide, although the side products are not readily separable from the reaction

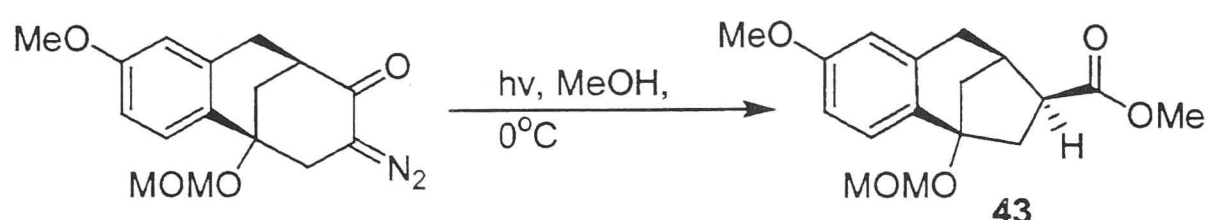
mixture. Utilisation of the Regitz method with *p*-nitro-benzenesulfonyl azide led to yields of 55-60% for the diazoketone **53** over the two steps (Scheme 2.12).

Scheme 2.12

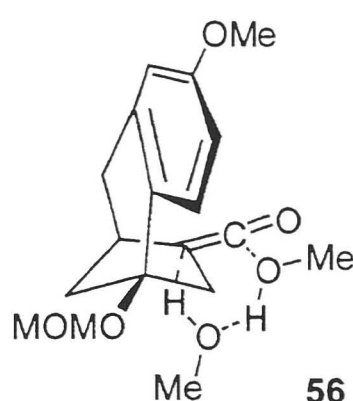


With the diazo ketone in hand, the Wolff ring contraction of this material to the methyl ester was explored (Scheme 2.13). It was found that it was essential to perform this reaction at high dilution (2g/L), to avoid unwanted side reactions such as dimerisation of the intermediate ketene. On a small scale, a 125 Watt medium pressure mercury vapour lamp was used, but as the scale was increased, it was not powerful enough to complete the reaction in a reasonable time, so a 450 Watt medium pressure lamp was used for reactions on more than 500mg. With the larger lamp, it was found that 10 grams of diazoketone would be consumed within 5 hours.

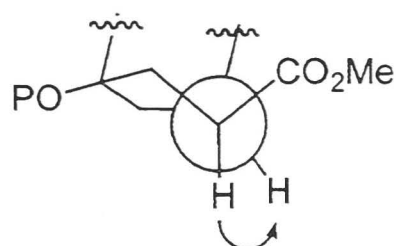
Scheme 2.13



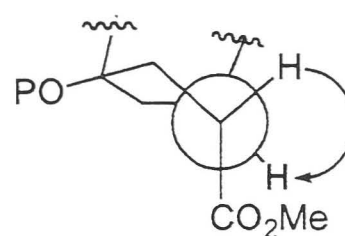
The ester formed in the reaction was a 10:1 mixture of epimers, with the *endo* adduct **43** being favored. Preference for this isomer was rationalised as being due to methanol approaching from the lower face of the ketene intermediate, as the aromatic ring sterically hinders the upper face of the molecule, as shown in transition state **56**.



Several features in the ^1H NMR spectrum led to the conclusion that the *endo* adduct was the predominant epimer. First, the chemical shifts for the methoxy ester protons were significantly different. The major isomer was at 3.62 ppm, while the minor isomer was at 3.71 ppm. This difference is consistent with the methoxy group of the major isomer being shifted upfield due to shielding by the aromatic ring. Secondly, the signal for the proton alpha to the ester (H7) was at 3.26 ppm for the major isomer, indicating that it was not being shielded by the aromatic ring. It also showed a larger coupling constant to the bridgehead proton ($J = 7.3$ Hz major isomer, $J = 0.0$ Hz minor isomer).



Endo isomer (major)
Dihedral angle approx. 35°
 $J =$ approx 7 Hz

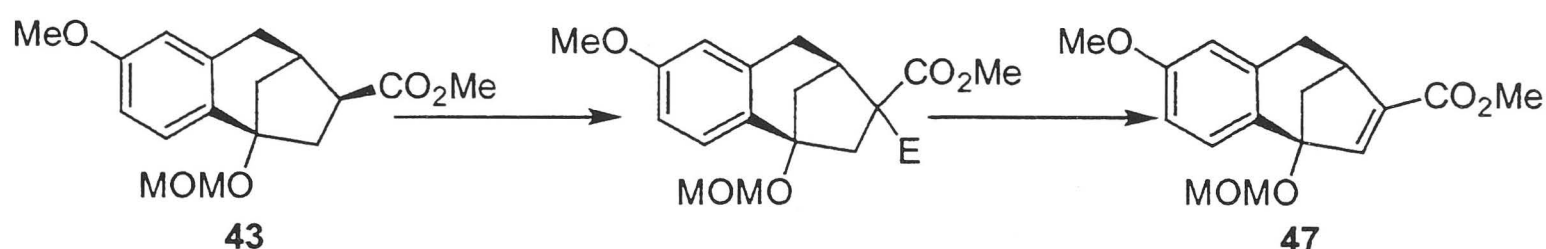


Exo isomer (minor)
Dihedral angle approx. 90°
 $J =$ approx 0 Hz

2.3 Synthesis of a suitable dienophile

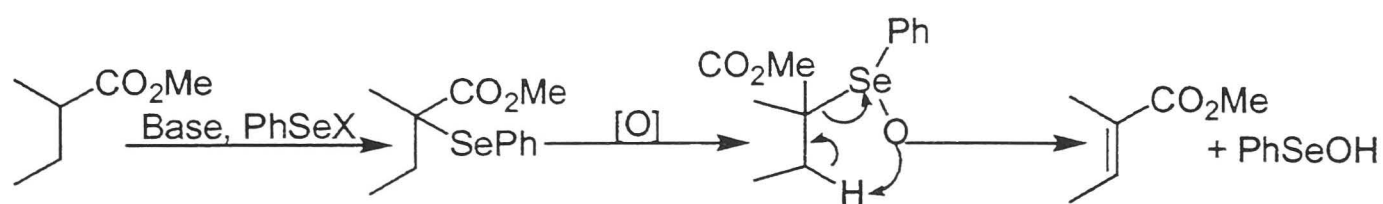
With the [3.2.1]bicyclononane in hand, the Diels-Alder reaction for the elaboration of the decalin rings was explored next. The ester function was ideally suited for the introduction of the alkene bond necessary for the planned Diels-Alder reaction. Enolisation of the ester, with subsequent trapping of the enolate with a suitable electrophile, followed by elimination of the electrophile could be expected to lead to the dienophile required for the Diels-Alder reaction (Scheme 2.14).

Scheme 2.14



Of the multitude of electrophiles available, a selenium derivative appeared to be the most suitable option as it is usually easily installed using diphenyl diselenide²⁶ or a phenylselenenyl halide.²⁷ Once installed, the selenide is reasonably stable, but can be oxidised to the selenoxide, which undergoes a *syn* elimination under very mild conditions to give the alkene (Scheme 2.15).²⁸

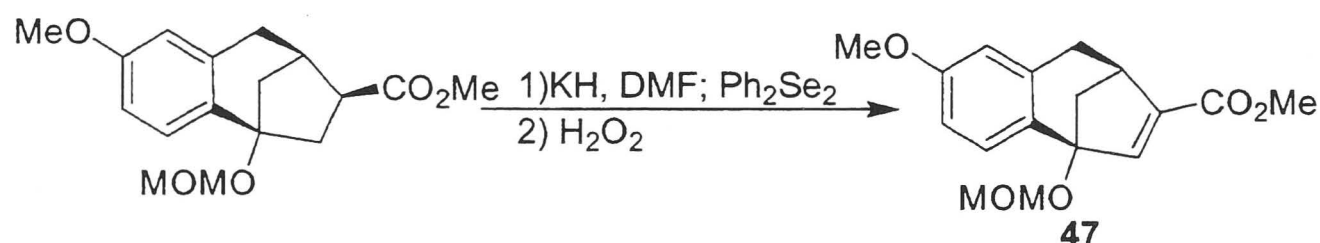
Scheme 2.15



The ester proved to be difficult to enolise, with most common bases returning only starting material. LDA gave trace amounts of the α -selenide, while treatment with KH in DMF, followed by addition of diphenyl diselenide gave a mixture of the selenide and the starting material (Scheme

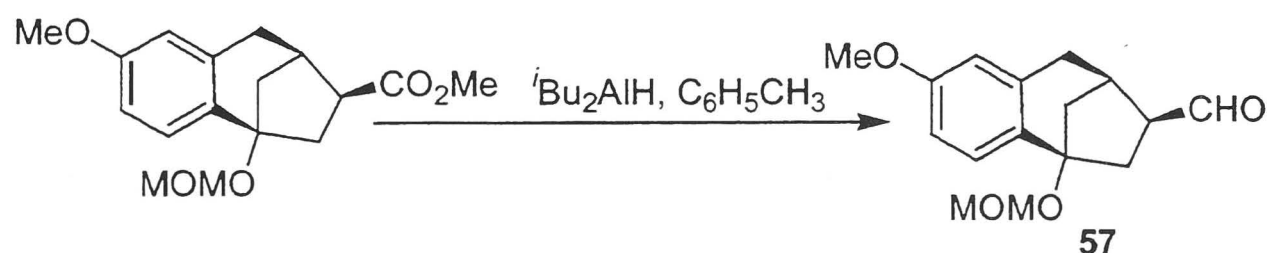
2.16). After oxidation with hydrogen peroxide less than 30% of the alkene **47** could be isolated.

Scheme 2.16



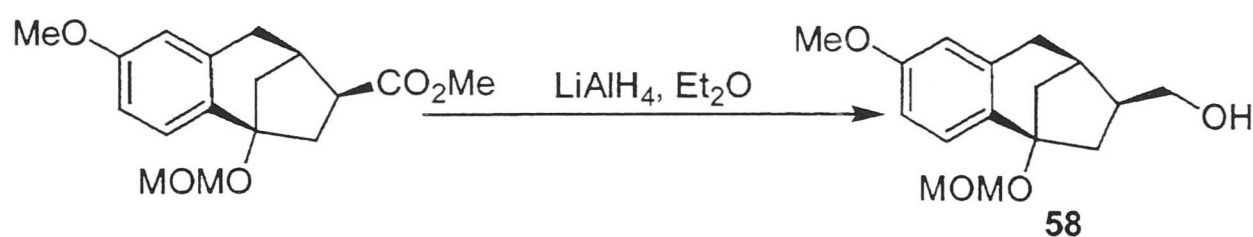
Since the ester was proving to be difficult to enolise, it was decided to employ the corresponding aldehyde **57**, which was expected to be more reactive. Treatment of the ester with one equivalent of DIBAL gave a 60-80% yield of the aldehyde directly (Scheme 2.17), but this could be improved if a two-step procedure was used instead.

Scheme 2.17



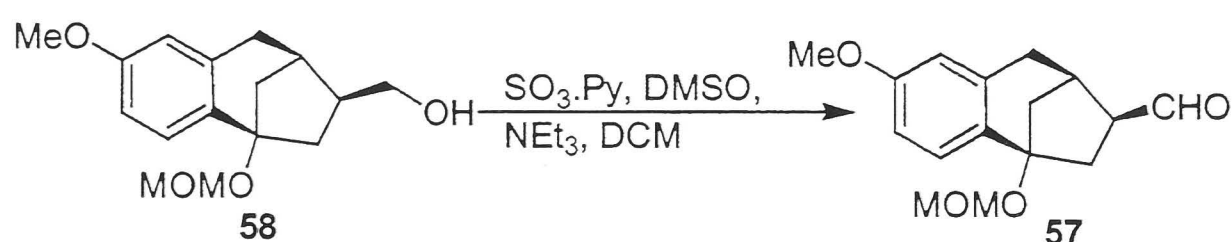
Reduction of the ester with LiAlH₄ gave a quantitative yield of the corresponding alcohol **58** (Scheme 2.18). Oxidation of the alcohol to the aldehyde was not so straightforward. PCC gave only a 59% yield of the aldehyde. Swern oxidation was ineffective and none of the desired product could be isolated. Dess-Martin periodinane was much better, and gave a greater than 95% yield. However, the synthesis of this reagent is dangerous and lengthy.²⁹

Scheme 2.18



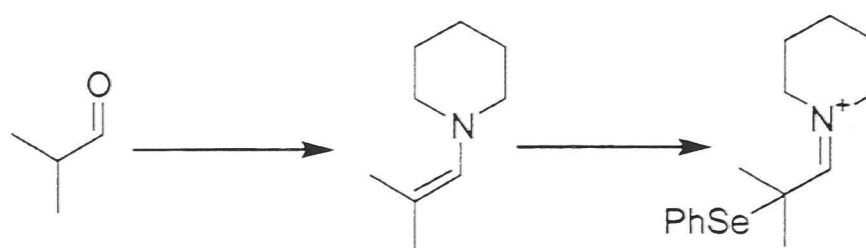
The best reagent for this reaction was DMSO-sulfur trioxide/pyridine complex, also known as the Parikh-Doering reagent (Scheme 2.19).³⁰ This reagent also gave a greater than 95% yield of the aldehyde in less than 1 hour and with off the shelf reagents. It was found that if the Parikh-Doering oxidation was left for more than an hour an unwanted byproduct was observed and accumulated rapidly at the expense of the desired product.

Scheme 2.19

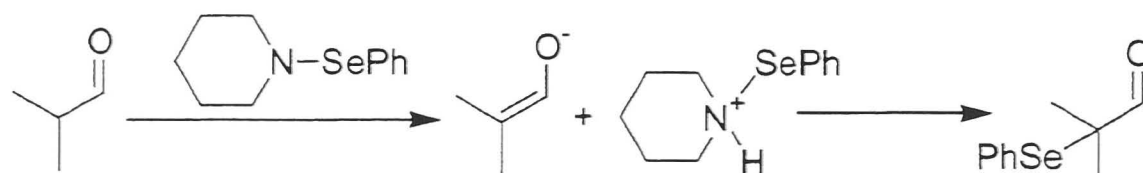


The aldehyde was much more reactive and the α -selenide could be formed by treatment of the aldehyde with piperidine and phenylselenenyl chloride (Scheme 2.22). There are two possible mechanisms for this selenation: either initial formation of an enamine, followed by attack of the phenyl selenium chloride (Scheme 2.20),³¹ or prior formation of phenyl selenamide, which can act as a base and deprotonate the aldehyde, followed by transfer of the electrophilic selenium (Scheme 2.21).³² A third possibility, that free piperidine acts as the base is unlikely, as phenyl selenium chloride reacts rapidly with amines at room temperature.³³ This last fact makes it more likely that the reactive species in this reaction is selenamide, although enamine formation cannot be ruled out.

Scheme 2.20

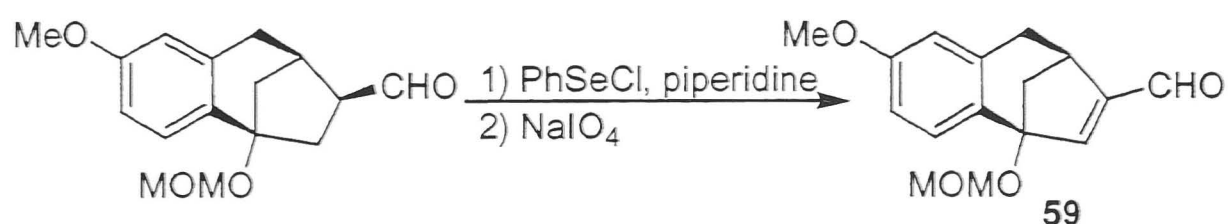


Scheme 2.21



Standard conditions for the oxidation of selenium employ hydrogen peroxide, but it was found that the selenic acid that is formed could react further with the hydrogen peroxide to form peroxyselenic acid,³⁴ which readily oxidized the aldehyde to the corresponding carboxylic acid. This problem was readily circumvented by the use of sodium periodate, which formed the selenoxide rapidly. The selenoxide readily underwent elimination *in-situ* to give a high yield (84%) of the enal **59** upon workup and purification (Scheme 2.22).

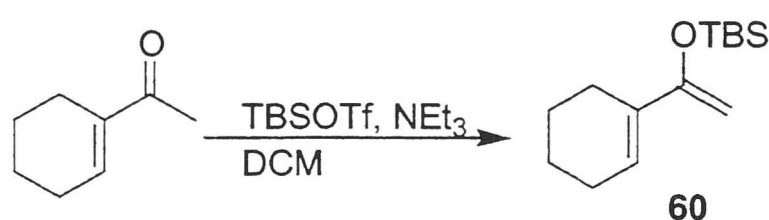
Scheme 2.22



2.4 The Diels-Alder reaction

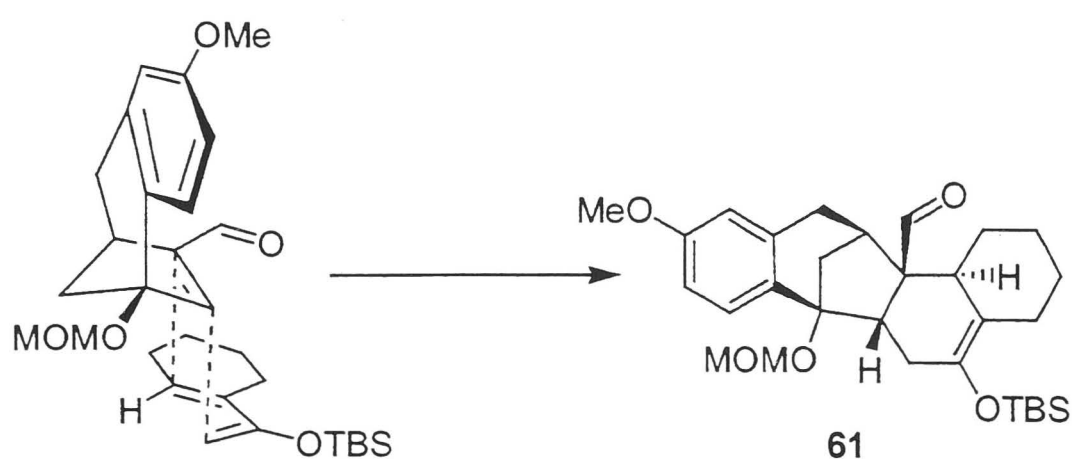
With a suitable dienophile now in hand, it was time to explore the pivotal Diels-Alder reaction. The required diene **60** had been synthesized previously by several groups,³⁵ the best procedure being the treatment of 1-acetylcyclohexene with TBSOTf and NEt₃, followed by distillation (Scheme 2.23).

Scheme 2.23



It was expected that the Diels-Alder reaction would have high regioselectivity for the desired “*para*” product **61** shown in Scheme 2.24. The stereochemical outcome was expected to be determined by two factors, the *endo* transition state shown in Scheme 2.24, which is well recognized as being more favourable for the Diels-Alder reaction, and the approach trajectory, which should be to the lower face of the dienophile, since the upper face is blocked by the aromatic ring.

Scheme 2.24



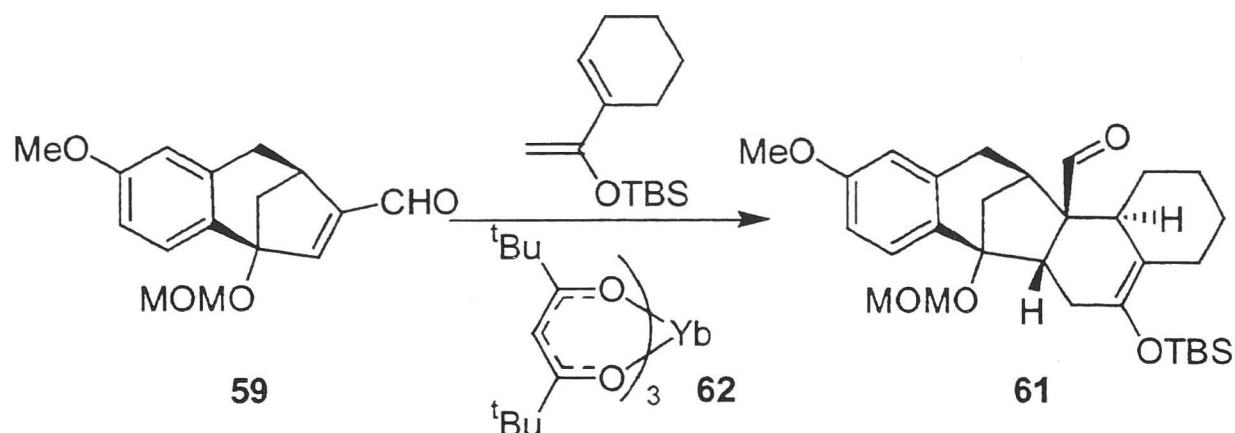
Heating the diene and the dienophile together in toluene at reflux overnight resulted in the formation of about 60% of the desired adduct **61**, although

there were several other spots by TLC, which ^1H NMR spectroscopy indicated may have been diastereoisomers or isomerisation products.

It is well recognized that Lewis acids can accelerate the rate and increase the selectivity of Diels-Alder reactions. The use of traditional Lewis acids can result in polymerization of the starting materials, but the lanthanides have been shown to be less likely to do this, so it was decided to investigate the use of the lanthanides as catalysts for this Diels-Alder reaction.³⁶

The use of ytterbium(III) triflate ($\text{Yb}(\text{tf})_3$) as a catalyst resulted in a slow reaction at room temperature to give about 20% of the Diels-Alder adduct after 16 hours. Heating the $\text{Yb}(\text{tf})_3$ catalysed reaction resulted in decomposition of the starting materials, indicating that this catalyst was too acidic, so the catalyst, ytterbium tris(2,2,6,6-tetramethyl-3,5-heptanedionate) ($\text{Yb}(\text{thd})_3$) **62**, was tried instead. Stirring the Diels-Alder reaction at room temperature with $\text{Yb}(\text{thd})_3$ resulted in no product formation, but if the reaction was heated at 83°C in 1,2-dichloroethane at reflux, all of the dienophile was consumed after 16 hours, and only one product could be observed by TLC and ^1H NMR spectroscopy (Scheme 2.25). The yield of the Diels-Alder reaction appeared to be dependent on scale and ranged from about 75% for small scale reactions, up to 90% for quantities of dienophile greater than one gram.

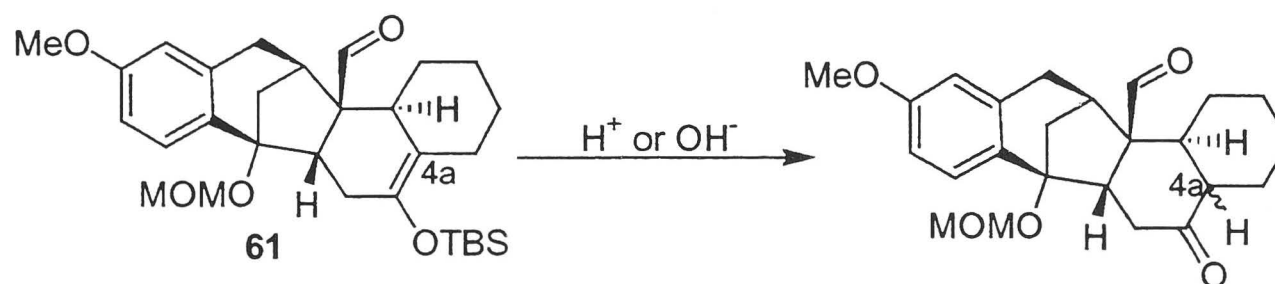
Scheme 2.25



The silyl enol ether function in the product **61** was reasonably stable, but silica gel catalysed the isomerisation of the double bond to a small extent to give a mixture of enol ethers that were diastereomeric at C4a. The use of 1% NEt_3 in the eluent during column chromatography suppressed this isomerisation. Attempts to deduce the stereochemistry of the adduct were hindered by the complex nature of the ^1H NMR spectrum, which had multiple overlapping signals in the aliphatic region.

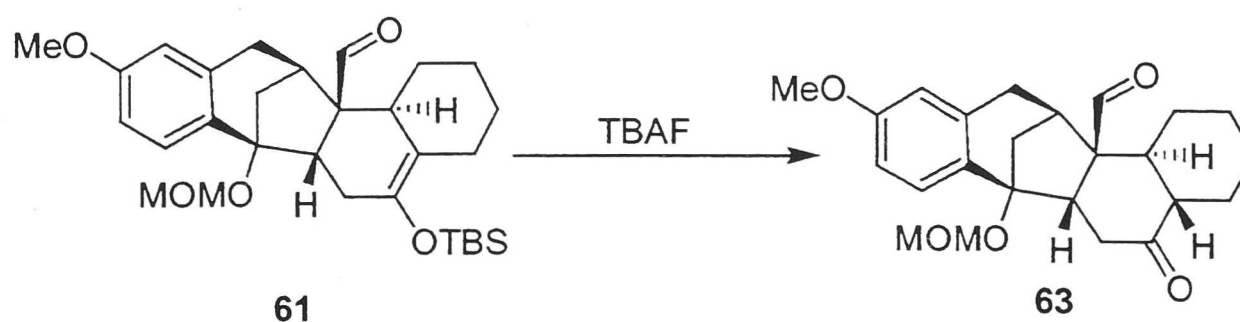
Hydrolysis of the silyl enol ether **61** was attempted next. The use of either aqueous HCl or aqueous base resulted in low yields of the ketone and epimeric mixtures at C4a (Scheme 2.26).

Scheme 2.26



Although attempts to equilibrate the epimers with organic amine bases were not successful, this problem could be avoided by the use of TBAF at 0°C to hydrolyse the enol ether, as this cleanly gave one product **63**, which was crystalline (Scheme 2.27). Attempts to purify this material by column chromatography were hindered by low solubility in ethyl acetate/petroleum spirit elutants, but the use of 50% DCM in the eluant circumvented this problem.

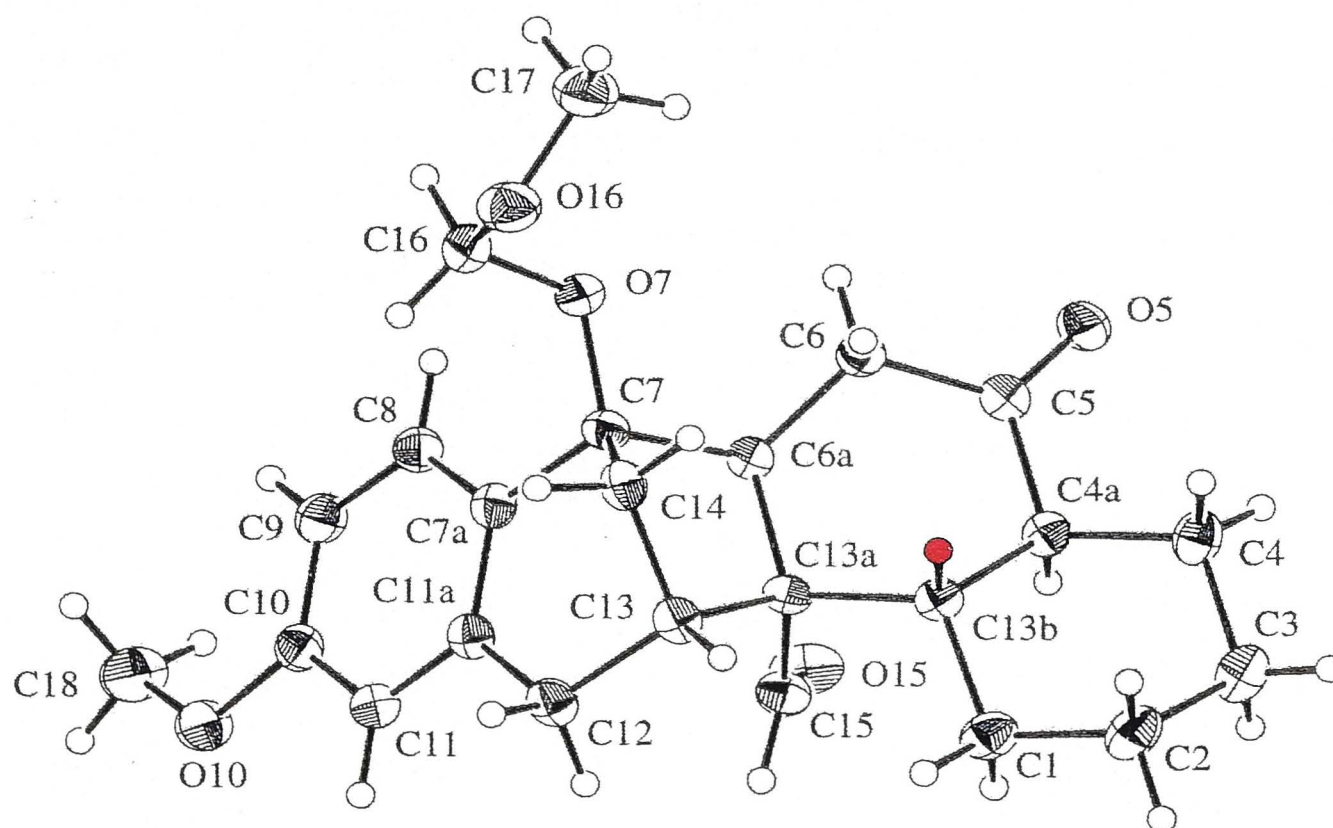
Scheme 2.27



With the crystalline ketone in hand it was possible to obtain an X-ray crystal structure, which allowed unambiguous determination of the stereochemistry of the Diels-Alder adduct. The analysis confirmed that the Diels-Alder reaction had proceeded with the expected stereoselectivity to give the desired adduct **61**, and that hydrolysis of the silyl enol ether had given the *trans* ring junction.

The ORTEP diagram is shown in Figure 2.1 and the proton attached to C13b is colored red. This clearly shows that H13b is *anti* to the aldehyde function. The X-ray structure also shows that the internal ring of the decalin system is in the boat configuration. This explains why attempts to equilibrate the diastereoisomers at C4a were unsuccessful, as the energies for the two isomers are much closer than would be the case for the corresponding chair conformations.

Figure 2.1: The ORTEP diagram for compound **63** ³⁷



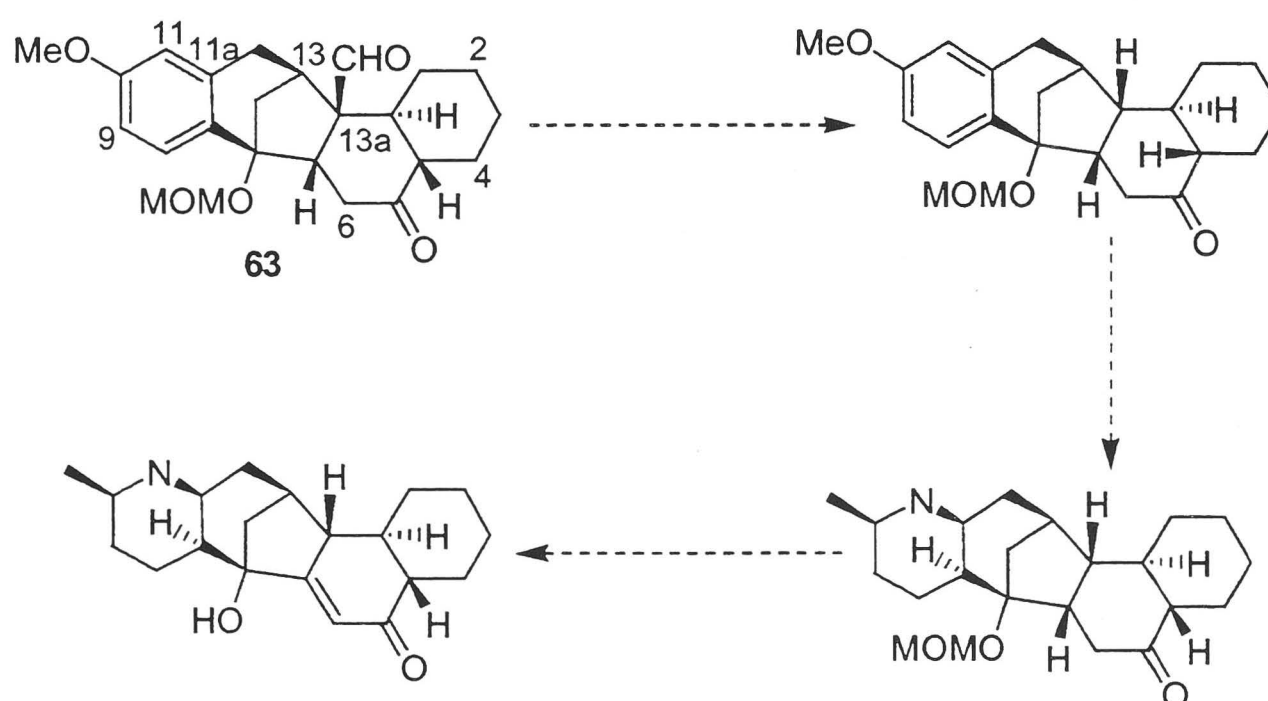
Chapter 3

Removal of the superfluous C13a substituent

3.1 The decarbonylation approach

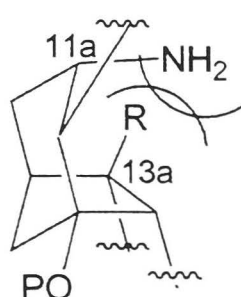
With the pentacyclic ring system of the natural products largely constructed there were three major tasks left to complete. The surplus carbon at C13a that was used to direct the Diels-Alder reaction must be removed, the aromatic ring must be converted to the methyl piperidine ring of the natural product and the unsaturated ketone moiety must be formed (Scheme 3.1). These transformations must be carried out in the order outlined above for several reasons.

Scheme 3.1



First, the substituent at C13a is likely to interfere with any reactions performed on the aromatic ring, due to the close proximity of this group to C11a. In addition, the required axial amino group at C11a would also be in very close proximity to any substituent at C13a (Figure 3.1).

Figure 3.1

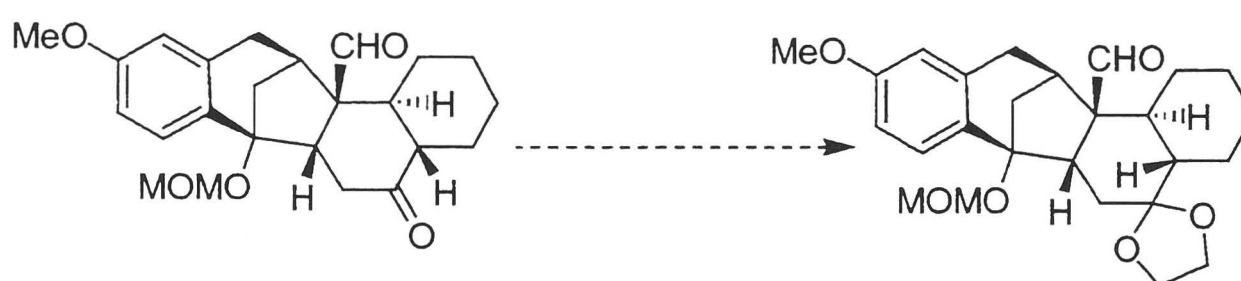


The aromatic ring requires forcing conditions for reduction and an unsaturated ketone would not withstand these conditions. With these concerns in mind, methods for the removal of the superfluous substituent in question were explored. The most common methods for cleaving carbon-carbon bonds are by decarboxylation, a retro-aldol or retro-Claisen type of conversion, or a transition metal catalysed decarbonylation.

The use of a transition metal complex such as Wilkinson's catalyst to perform decarbonylations is well known.³⁸ However, there are several restrictions to this method, including the requirement for stoichiometric quantities of the transition metal complex, and of the most relevance to this synthesis, the low reactivity of the catalyst with hindered substrates. There are several examples of decarbonylation of tertiary aldehydes in the literature,³⁹ but these are generally acyclic and have one or more aryl substituents, with the reduction in steric bulk that this brings. Despite the lack of precedent, it was felt that this reaction should be attempted, as it was the simplest of the methods available.

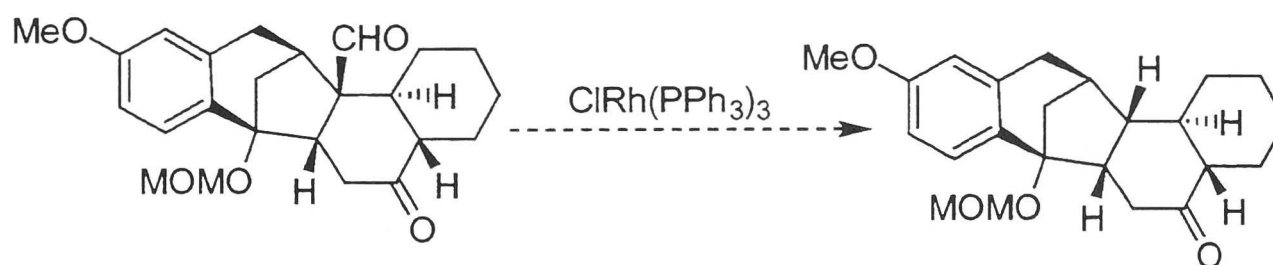
Before an attempt could be made on decarbonylation, the carbonyl function at C5 should be protected to reduce the possibility of side reactions (Scheme 3.3). Unfortunately, all attempts to protect this carbonyl function using literature procedures involving ethylene glycol with molecular sieves⁴⁰ or ortho esters,⁴¹ Noyori conditions,⁴² or nucleophilic processes using 2-bromoethanol⁴³ returned only starting material or decomposition products. Similarly, using 2,2-dimethylpropane-1,3-diol instead of ethylene glycol also failed to give any of the desired ketal.

Scheme 3.3



Although the carbonyl function at C5 could not be protected, it was thought that Wilkinson's catalyst might still perform the desired decarbonylation (Scheme 3.4). Heating the aldehyde at reflux in toluene with Wilkinson's catalyst for 24 hours, however, returned only starting material. The solvent was changed to 1,3,5-trichlorobenzene and the reaction was heated to 200°C, at which point the starting material decomposed without any sign of the desired decarbonylated product being formed. From this result it appeared that the compound was indeed too hindered to react with Wilkinson's catalyst, so a new method was sought.

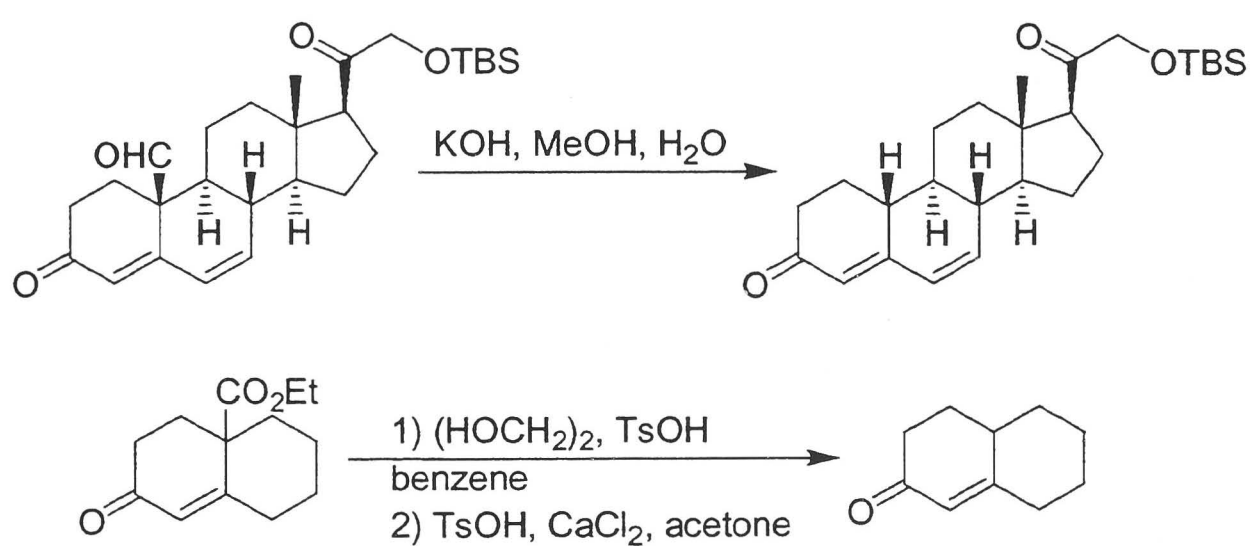
Scheme 3.4



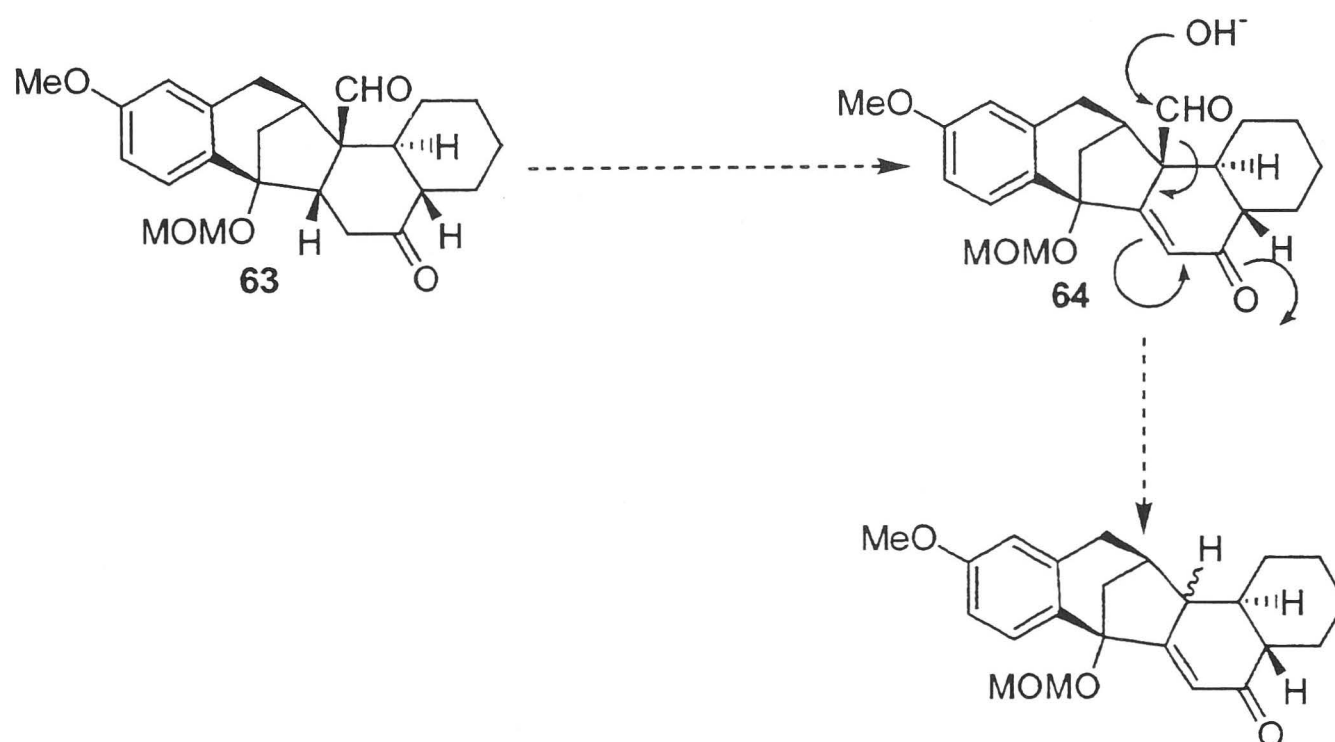
3.2 The retro-Claisen approach

The second attempt at removing the aldehyde group focused on the retro-Claisen reaction, which can be catalysed by either acid or base, as can be seen from the following literature examples in Scheme 3.5.⁴⁴ This approach required the prior formation of the α,β -unsaturated ketone **64** (Scheme 3.6), which will be discussed next.

Scheme 3.5



Scheme 3.6

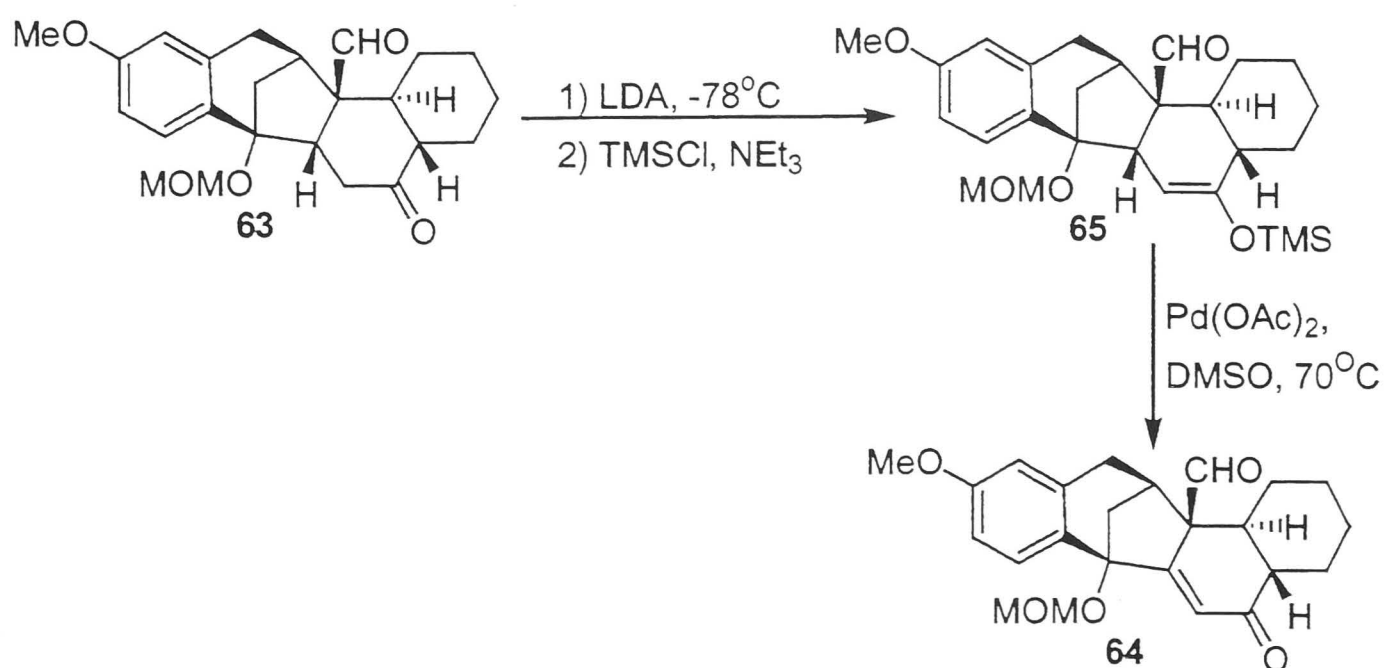


There are many methods for the conversion of saturated ketones to enones, some of which were addressed in Chapter 2, Section 3. Many of these methods are not applicable in this case, as the ketone can enolise in two different directions and the incoming electrophile can approach from either face of the molecule. Moreover, the hydrogen atom that must be eliminated is very hindered, and may not afford the desired orbital overlap for ready elimination.

These problems could be largely overcome by dehydrosilylation of the corresponding silyl enol ether, as there are well-established methodologies for the selective enolisation of ketones,⁴⁵ while the planar nature of the silyl enol ether circumvents any issues with diastereoselectivity and orbital alignments.

To this end, the "kinetic" silyl enol ether of the C5 ketone was formed by treatment of the ketone **63** with LDA, followed by trapping of the enolate with TMSCl and NEt₃. The silyl enol ether **65** was then oxidatively desilylated⁴⁶ with Pd(OAc)₂ in DMSO at 70°C to give a mixture of the α,β -unsaturated ketone **64** and the starting ketone (Scheme 3.7).

Scheme 3.7

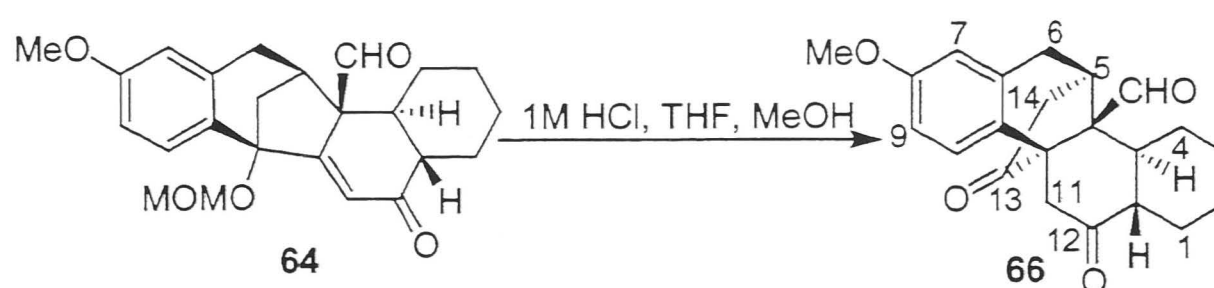


After purification of the enone **64** by column chromatography, the retro-Claisen reaction was attempted with a variety of acids and bases. K_2CO_3 in THF/MeOH/ H_2O did not react with the enone at room temperature, while heating at reflux resulted in decomposition. Likewise, NaOMe returned only decomposed material, with the aldehyde peak still apparent in the 1H -NMR spectrum.

Treatment with *p*-toluenesulfonic acid in MeOH at room temperature, or at reflux, gave no reaction, but when the solvent was changed to the higher boiling point solvent mixture, ethylene glycol/toluene, several inseparable products were formed, including some products that appeared to contain the ethylene ketal functional group, by 1H -NMR spectroscopy. Unfortunately, the aldehyde peak was still apparent in the 1H -NMR spectrum, and the MOM group had been lost.

When the retro-Claisen reaction was attempted using aqueous HCl in THF/MeOH at room temperature, the reaction returned one major product, **66**, which was very different to the starting material (Scheme 3.8). After analysing several spectra it became apparent that a 1,2 alkyl shift analogous to the one that had been observed for alkaloid GB 13⁴⁷ was also taking place with this substrate (Scheme 3.10). Both signals for the MOM group and the alkene function were absent from the 1H -NMR spectrum, while the aldehyde peak was still apparent. Also, there were signals for three AB methylene systems in the 1H -NMR spectrum.

Scheme 3.8

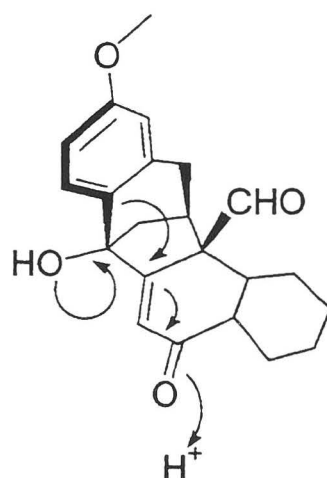


The three AB systems observed in the ^1H -NMR spectrum were at 2.21 and 2.71 ppm, attributed to H14 and H'14, 2.89 and 3.40 ppm for H6 and H'6, and 3.04 and 3.55 ppm for H11 and H'11. These assignments were aided by the fact that both H14 and H6 are adjacent to the bridgehead hydrogen, H5, so they showed a small coupling of less than 8 Hz to this hydrogen; H6 and H'6 are attached to a benzylic carbon and so should be observed downfield from H14 and H'14.

Further evidence for the rearrangement came from an APT ^{13}C -NMR spectrum, where two peaks were observed at 207.3 and 208.2 ppm with a positive value, which is where the peaks for the two postulated ketone carbonyl groups at C12 and C13 should appear. A third signal at 202.8 ppm with a negative value was observed, and could be attributed to the aldehyde carbon. Assessments based on the IR spectrum of the compound were inconclusive, as only 2 peaks could be observed, one at 1744 cm^{-1} and the other at 1710 cm^{-1} .

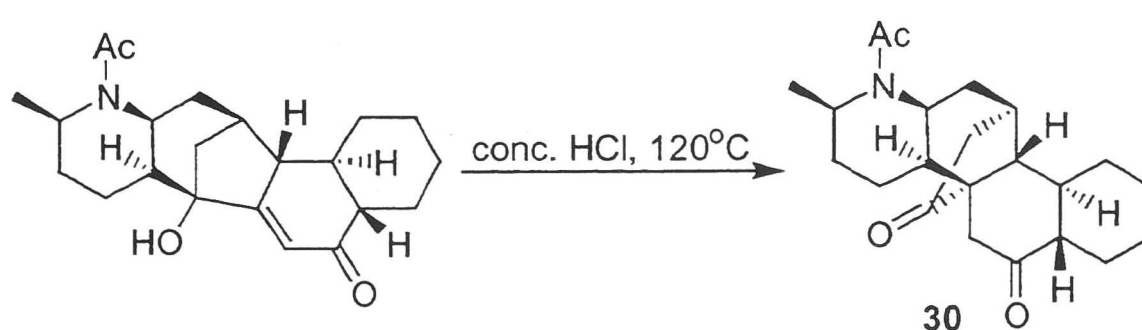
In retrospect, it was obvious that this rearrangement was highly favoured, due to the rigidity of the [3.2.1]bicyclononane system and the planarity of the enone that allows good overlap of the interacting orbitals, as shown in Figure 3.2. This rearrangement is thermodynamically favoured due to the increased stability, by about 20 kcal., of the newly formed diketone, relative to the enone. Moreover, some of the ring strain is released by conversion of the sterically encumbered bridgehead hydroxyl group to a ketone, which has a much lower steric demand due to its sp^2 nature.

Figure 3.2



In addition, this system could be expected to be far more reactive than GB 13, by virtue of the aromatic ring. The rearrangement of alkaloid GB 13 requires heating in concentrated HCl at reflux (Scheme 3.10), while this system undergoes the equivalent rearrangement at room temperature and in dilute HCl. This difference is not surprising, as it could be expected that the aromatic substituent should migrate much more readily than the alkyl group of GB 13, as it has a far higher electron density, especially because of the *p*-methoxy substituent.

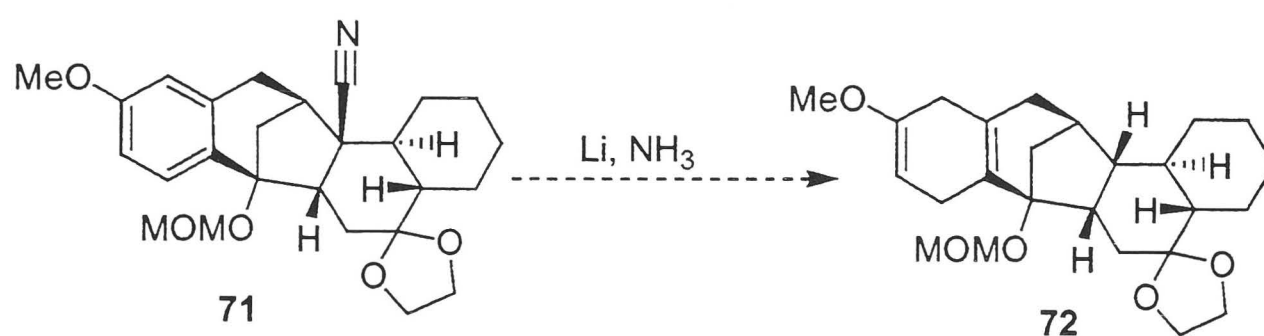
Scheme 3.10



3.3 The decyanation approach

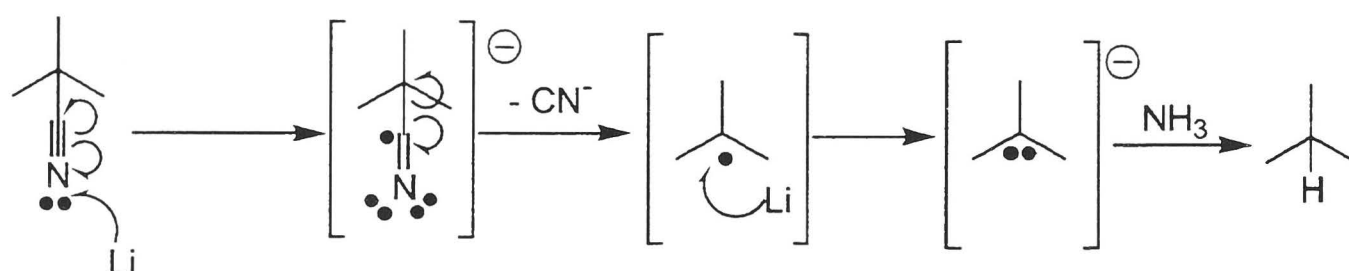
Since the retro-Claisen reaction was not performing as hoped, the use of radical based carbon-carbon bond cleaving reactions were investigated. While the use of Barton esters⁴⁸ was not precluded in this instance, a more direct option was the use of dissolving metal conditions to perform a decyanation. The attraction of this procedure was the possibility of removing the surplus carbon at C13a, and reducing the aromatic ring at the same time, as outlined in Scheme 3.11.

Scheme 3.11



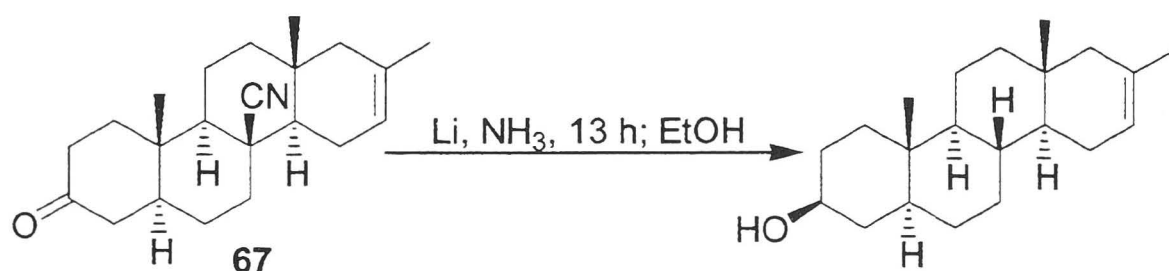
The decyanation proceeds, as outlined in Scheme 3.12,⁴⁹ through a one-electron reduction to give an intermediate radical anion, which then undergoes a homolytic cleavage of the carbon-carbon bond to give a cyanide anion and a tertiary radical. The radical is then further reduced by a second electron transfer to give an anion, which can abstract a proton from the solvent. Reduction of the aromatic ring cannot occur at this point unless a proton source such as an alcohol is present in the reaction mixture, as the intermediate radical anion is too weakly basic to abstract a proton from the ammonia solvent. Rapid quenching of the excess lithium with a relatively strong acid such as ammonium acetate only gives the decyanated product, while the addition of ethanol can protonate the aromatic radical anion, thus allowing Birch reduction of the aromatic ring.

Scheme 3.12



A recent example from the literature is the decyanation of the homo steroid **67** with lithium in liquid ammonia (Scheme 3.13),⁵⁰ which proceeded in 64% yield. Of note is the long reaction time required to effect this transformation, and the high selectivity for the more stable β stereochemistry at the reacting centre. The preference for this stereochemical outcome is due to the planar nature of the intermediate radical and the facile inversion of the stereochemistry of the intermediate anion during this reaction.

Scheme 3.13



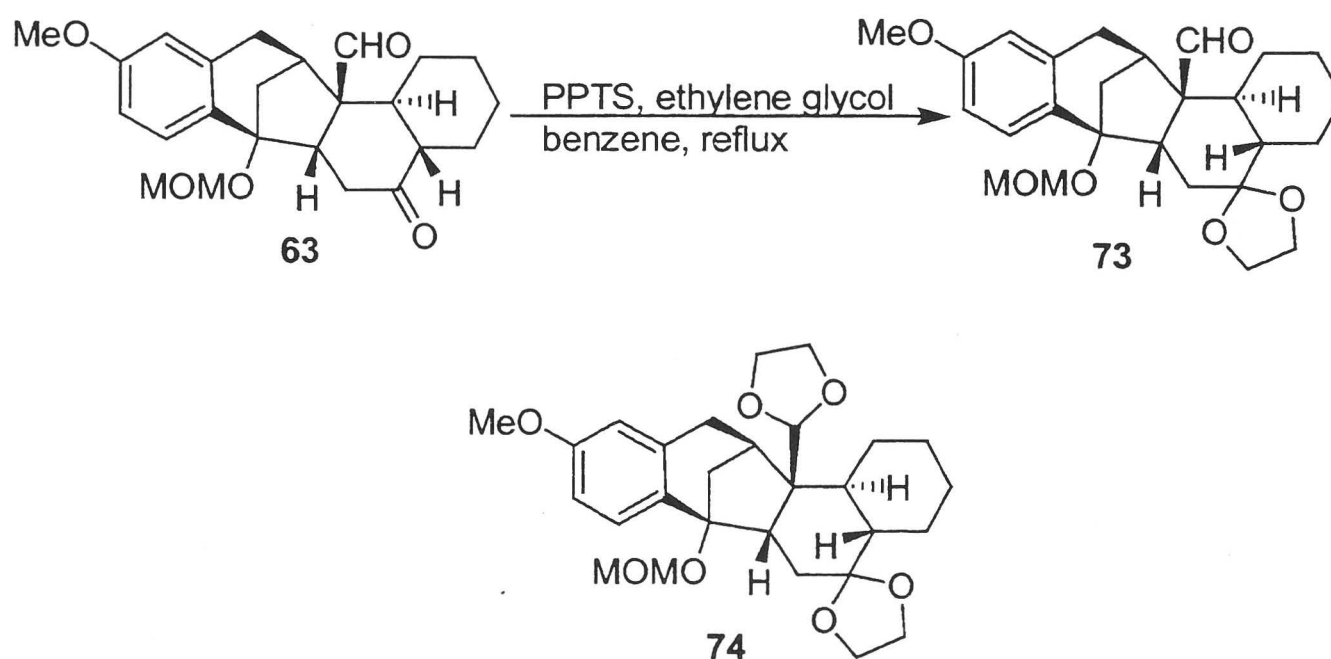
The anion expected to be formed in the desired decyanation of compound **71** will likely be quenched with retention of stereochemistry to give the desired product **72**, as the 5-6 ring junction has a strong preference for the *cis* stereochemistry.

Before the decyanation could be explored, the C5 ketone must be protected to allow conversion of the aldehyde to the nitrile and to prevent reduction of the ketone function during Birch reduction.

By analysing the earlier attempt at a retro-Claisen reaction using *p*-toluenesulfonic acid and ethylene glycol it was apparent that the ethylene

ketal could be formed, although a weaker acid catalyst would be required to prevent hydrolysis of the MOM group. Pyridinium tosylate was ideal, and it was found that heating a benzene solution of the keto aldehyde **63**, excess ethylene glycol and excess pyridinium tosylate at reflux in a Soxhlet apparatus for three days gave an 80% conversion to the mono acetal **73** (Scheme 3.15). If the reaction was left for a longer period the *bis* acetal **74** formed rapidly to become the sole product after four days.

Scheme 3.15

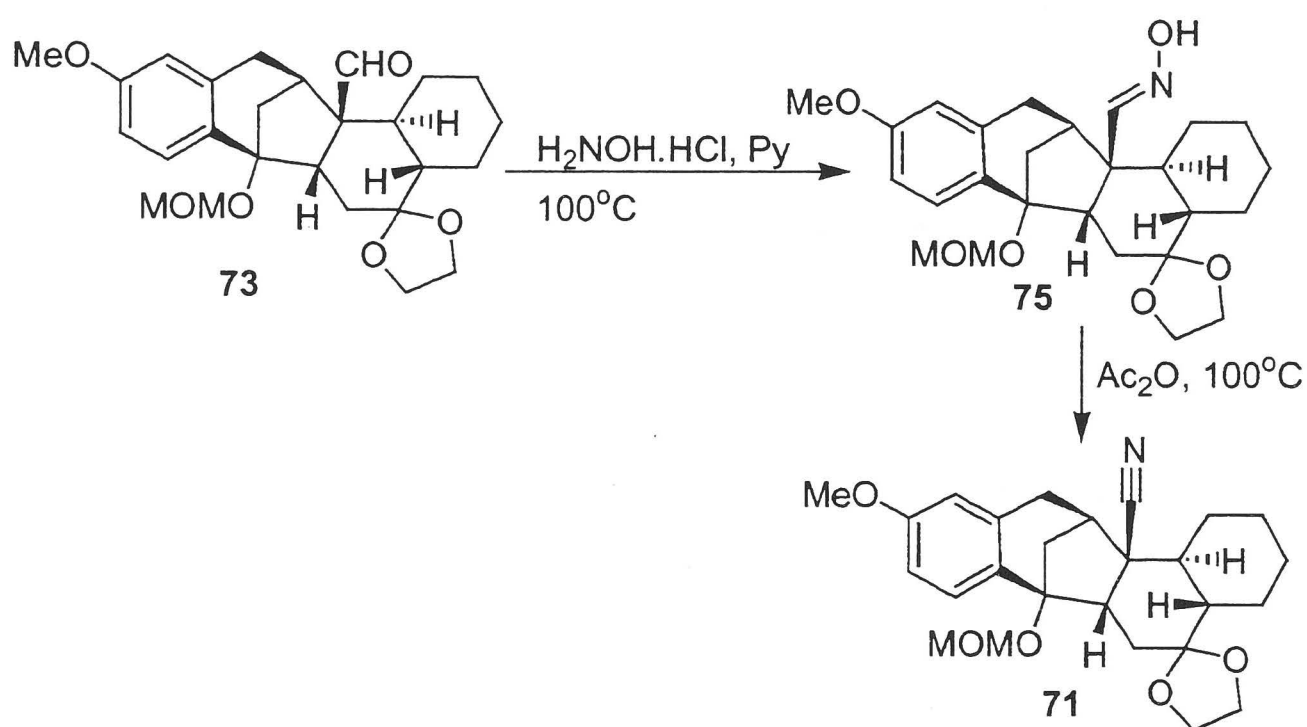


This result could be rationalised by assuming that the reaction is in equilibrium and acetal formation is disfavoured, due to the large excess of hydrophilic ethylene glycol, and that the aldehyde is so sterically hindered that there is a reversal of stability for the acetals, such that the ketone derived acetal is more stable. This results in a slow build up of the mono acetal until all the starting material has been consumed, followed by a slightly faster reaction to the bis acetal.

With the ketone protected, the aldehyde was converted to the corresponding oxime **75** in almost quantitative yield by heating at 100°C with hydroxylamine hydrochloride in pyridine for two hours. The oxime was isolated and then dehydrated by heating at 100°C in acetic anhydride to give

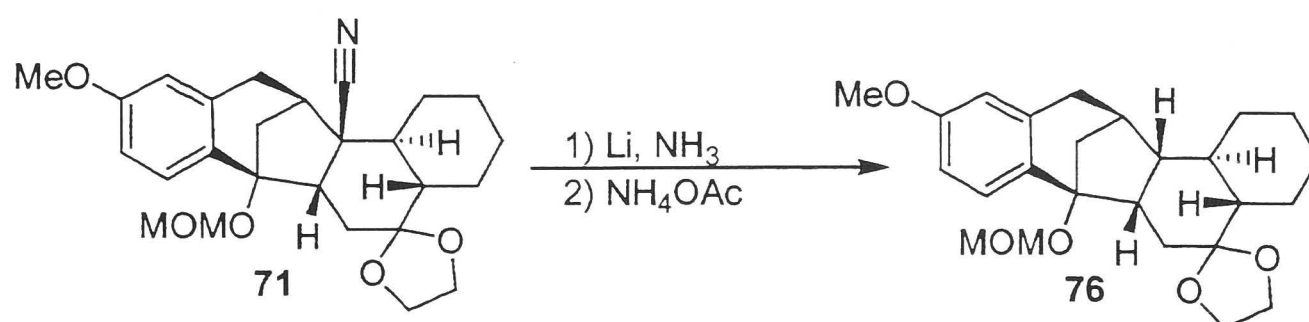
the nitrile **71** in a modest yield of about 40-60% (Scheme 3.16). Care was required in the quenching of this reaction as any acetic acid formed could readily hydrolyse the ethylene ketal.

Scheme 3.16



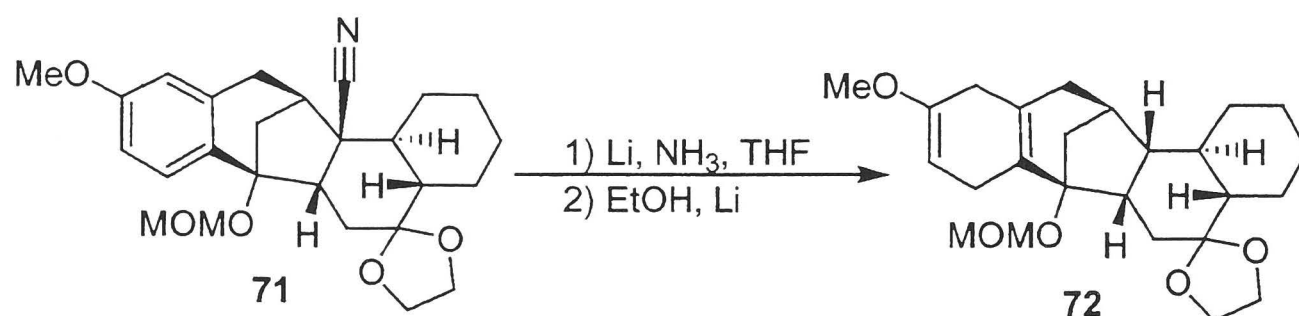
Treatment of the nitrile with a large excess of lithium in liquid ammonia for two hours followed by quenching of the reaction with solid ammonium acetate gave a near quantitative yield of the decyanated product **76** (Scheme 3.17).

Scheme 3.17



If the nitrile was treated as above, but the reaction was quenched with a large excess of ethanol, followed by the addition of more lithium over 20 minutes, then the unstable decyanated Birch reduced product **72** could be isolated (Scheme 3.18).

Scheme 3.18

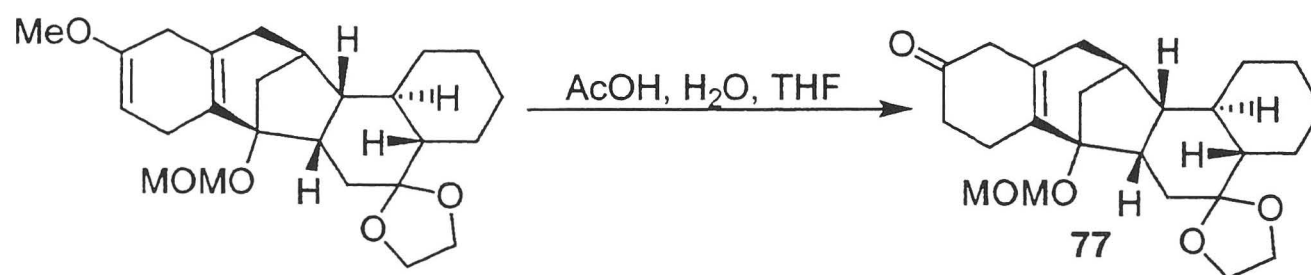


Evidence that the cyano group had been removed came from both the IR spectrum, which showed no evidence of a peak corresponding to a nitrile group near 2220 cm^{-1} , and NMR spectra of the compounds. The *syn* periplanar nitrile group is observed to perturb the environment of H6a in the ^1H -NMR spectra, with the signal for H6a coming at 2.71 ppm for compound 71. After the reductive decyanation to aromatic compound 76, the signal associated with H6a appeared to be shifted upfield, to about 2.25 ppm, indicating that the cyano group was no longer present. Unfortunately, the signal for H6a overlapped with other signals in this region of the spectrum.

Further exploration on the chemistry of this series of compounds was hindered by the extreme acid lability of the ethylene ketal protecting group. Conversion of the partially reduced benzene ring to the corresponding α,β -enone was required, in order to allow ring cleavage to a compound suitable for the synthesis of the required piperidine ring. Hydrolysis of the methyl enol ether requires acidic conditions, while conversion of the β,γ -enone to the α,β -enone can be achieved with either acid or base.

The methyl enol ether could be hydrolysed with acetic acid in water, with retention of the protecting groups to give the β,γ -enone 77 (Scheme 3.19). However, attempts to conjugate the double bond with acid always resulted in the loss of the ketal protecting group, while basic conditions returned only starting material or decomposition products.

Scheme 3.19



At this point there were two problems that needed addressing within the synthesis so far. The synthesis of the nitrile 71 was long and inefficient, requiring a series of redundant changes in oxidation state, and there were several low yielding steps. In addition, it was apparent that the ethylene ketal protecting group was too labile to survive the conditions required to finish the synthesis. The next chapter will discuss how these problems were solved.

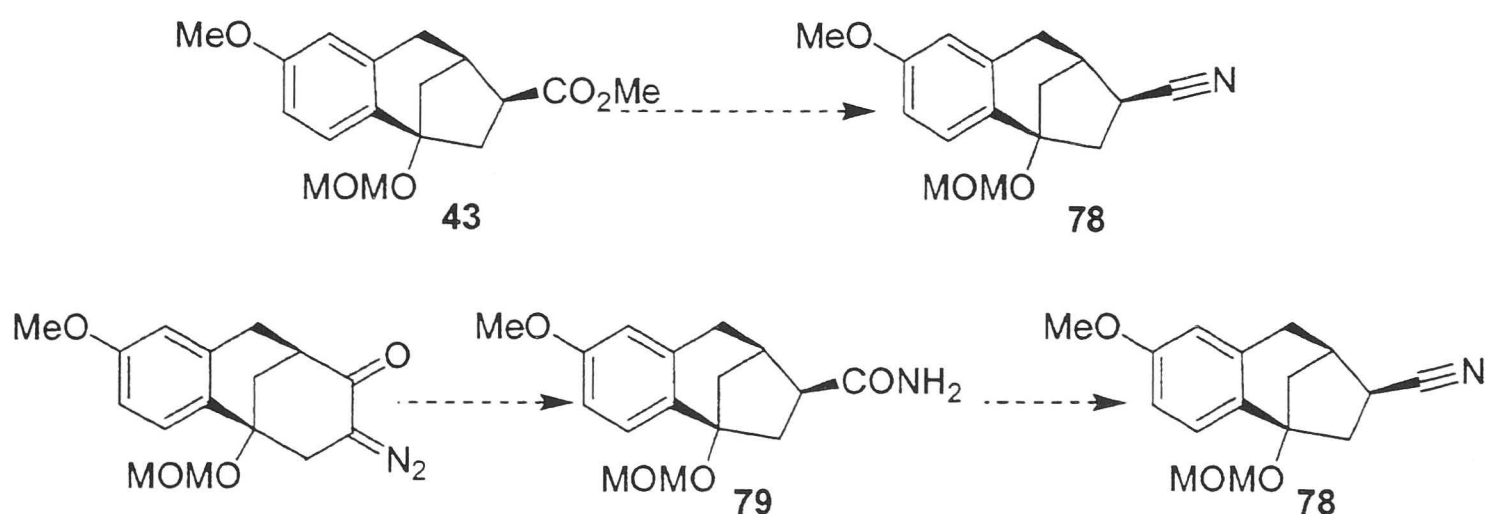
Chapter 4

An improved synthesis of the enone

4.1 Synthesis of pentacyclic nitrile 82

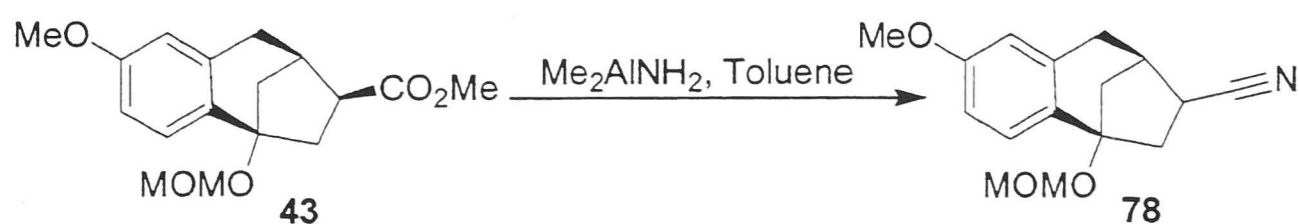
The previous synthesis of the nitrile 71 involved several redundant steps such as conversion of the ester to the aldehyde and conversion of the aldehyde to the nitrile. If the ester 43 could be directly converted to the nitrile 78 before the Diels-Alder reaction, several steps would be saved. Alternatively, the intermediate ketene in the Wolff ring contraction could be trapped with ammonia to give an amide, 79, which could then be dehydrated to the nitrile 78 (Scheme 4.1).

Scheme 4.1



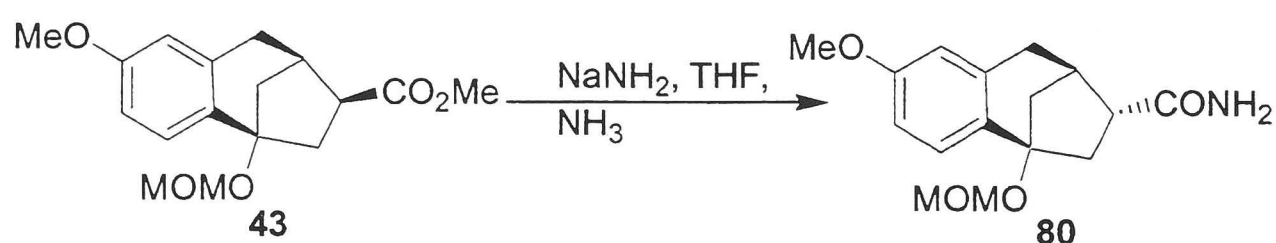
The direct conversion of esters to nitriles is a difficult transformation and only one procedure has been reported in the literature. This involves heating the ester with more than two equivalents of dimethyl aluminum amide at high temperatures and probably involves a carboxamide intermediate.⁵¹ Treatment of the ester 43 with three equivalents of dimethyl aluminum amide in toluene at reflux for 16 hours gave a 40% yield of the nitrile 78 on a small scale (Scheme 4.2). On a large scale though, the yield dropped to less than 10%.

Scheme 4.2



Since the direct synthesis of the nitrile from the ester was not efficient, the two-step procedure, *via* the analogous amide 79, was explored next. Aqueous ammonia failed to react with the ester, but sodium amide in ammonia did give 20-40% of the *exo* amide 80 (Scheme 4.3).⁵² This process was also too inefficient for use in this synthesis, so the use of ammonia in the Wolff ring contraction was explored next.

Scheme 4.3

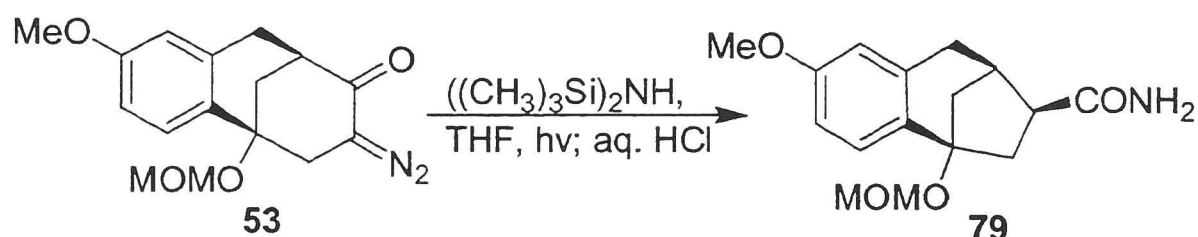


There is considerable literature precedent for the Wolff ring contraction to an amide,⁵³ although it is less common than the conversion to an ester. The choice of amine substituents is wide, ranging from aniline and benzylamine, to allyl, propargyl and simple alkyl groups, and even ammonia itself. The solvent can be either neat amine, or more commonly, due to the price of most amines, an inert solvent such as acetonitrile or THF. Once again, high dilution is necessary, particularly with a co-solvent, as the amine is in a lower concentration than the reactions performed neat, so the chances of side reactions occurring are increased.

Photolysis of diazo ketone 53 in liquid ammonia and THF gave a 57% yield of the *endo* amide 79, although the use of liquid ammonia presented practicality and safety issues on a large scale. Attempts to use benzylamine instead of ammonia gave very poor yields of the corresponding benzyl amide and in addition, required an extra step to remove the benzyl group. The best reagent for the desired transformation was hexamethyldisilazane,

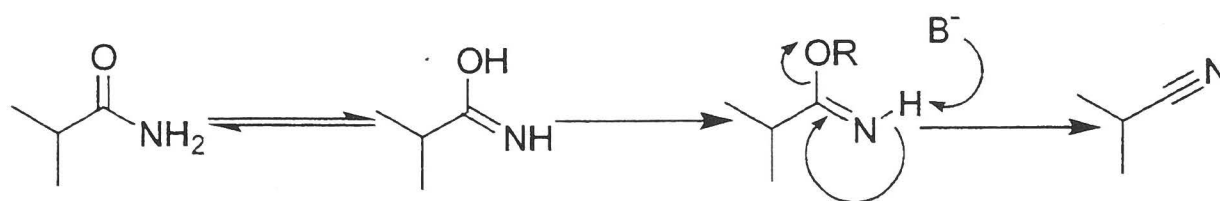
which gave a 62% yield of the amide after an acidic workup, which removed the labile silyl groups on the amide nitrogen (Scheme 4.4).

Scheme 4.4



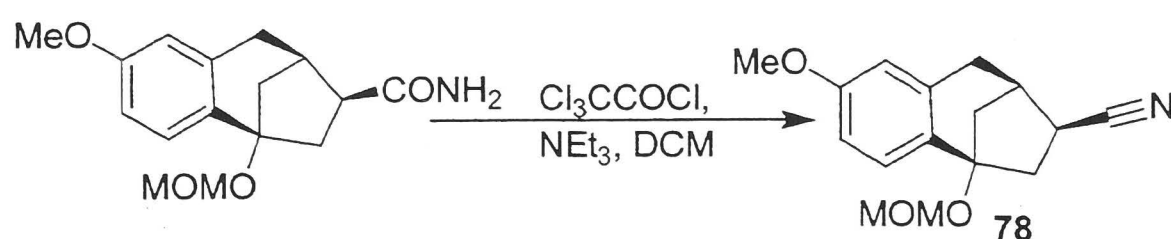
There are a multitude of reagents available for the conversion of amides to nitriles,⁵⁴ and most involve the formation of an iminyl derivative which can then undergo an elimination with a base (Scheme 4.5). Trichloroacetyl chloride and triethylamine is thought to react with amides through this mechanism.⁵⁵ The reagent is also cheap and readily available, so this method was the first choice for the required dehydration.

Scheme 4.5



The dehydration reaction of the amide with trichloroacetyl chloride and triethylamine gave the nitrile 78 in almost quantitative yield on the first attempt and continued to perform well upon scaling up (Scheme 4.6), so further exploration of this reaction was unnecessary.

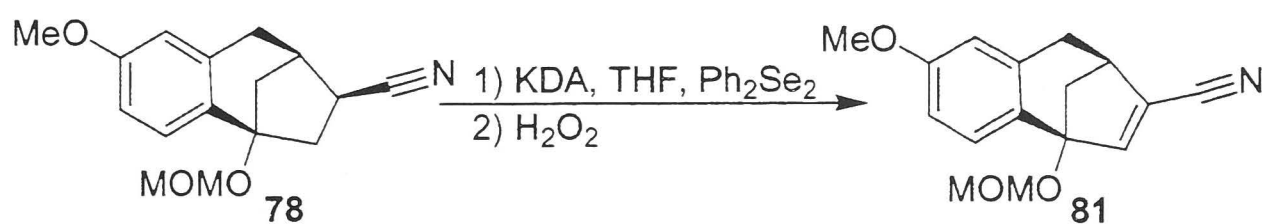
Scheme 4.6



With the nitrile **78** in hand the next step was installation of the double bond for the Diels-Alder reaction. The α positions of nitriles are weakly acidic, so it was likely that this nitrile would behave in a similar manner to the ester **43**, which gave only low yields of electrophilic addition products when treated with common bases and selenium derived electrophiles.

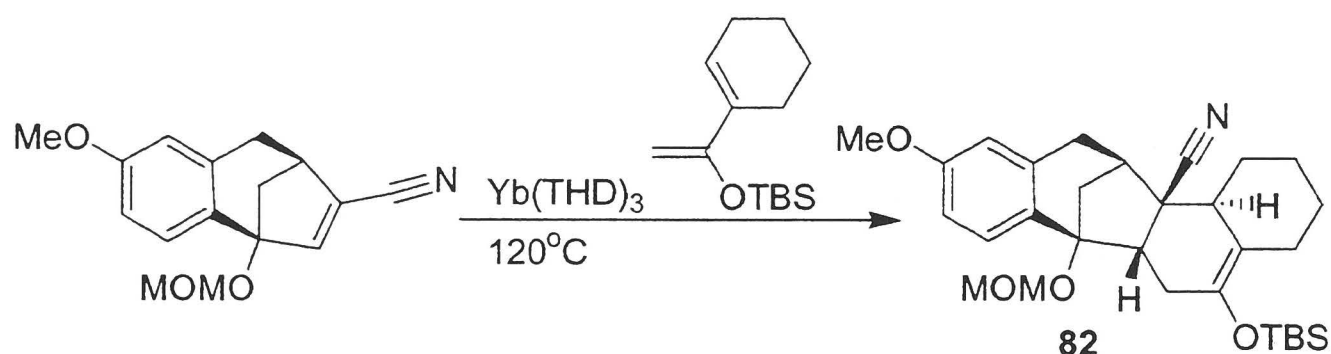
This proved to be the case, as treatment of the nitrile with LDA, followed by diphenyldiselenide or phenylselenenyl chloride and then an oxidant gave only modest yields of no more than 44% for the alkene **81**. This yield could be improved significantly by the use of KDA, which was made by the addition of a slight excess of potassium *tert*-butoxide to a solution of LDA.⁵⁶ KDA is reported to be more basic than LDA, and the enolate formed is also more reactive. We found this to be the case for imidate formation as well, since treatment of the nitrile with a threefold excess of KDA and a slight excess of diphenyldiselenide, followed by oxidation with hydrogen peroxide gave a 75-80% yield of the desired alkene **81** (Scheme 4.7).

Scheme 4.7



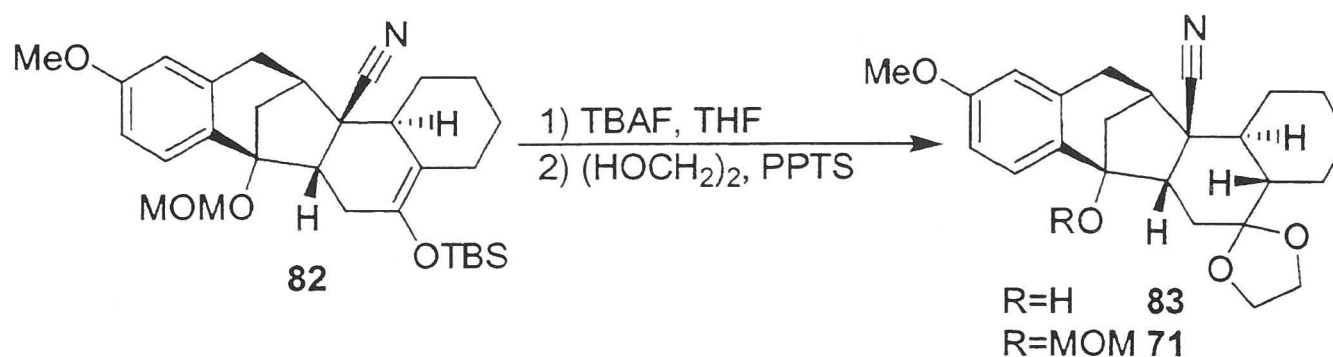
The nitrile was a far more sluggish dienophile in the Diels-Alder reaction than the corresponding aldehyde, and no reaction was observed after 24 hours at 80°C in DCE. However, changing the solvent to toluene and heating at reflux for 4 days gave a high yield of compound **82**. It was also found that the addition of $\text{Yb}(\text{thd})_3$ gave a 10% increase in rate. Omitting the solvent altogether and performing the reaction neat at 120°C further improved the reaction rate. The yield for this Diels-Alder reaction was equivalent to that of the analogous aldehyde **59** at 85-90%, and once again, no other isomers were observed in the ^1H -NMR spectrum (Scheme 4.8).

Scheme 4.8



The silyl enol ether **82** could be hydrolysed in high yield with TBAF and the ketone could then be protected as the ethylene ketal in the same manner as for the corresponding aldehyde **63**, to give the protected material **71** in 65% yield, as well as 20% of the MOM hydrolysed product **83** (Scheme 4.9). The material obtained from this sequence was identical to that obtained from the aldehyde series but in 3 fewer steps and with an increase in overall yield of 9.7% to 30.1% from the bicyclononanone **42**. The ethylene ketal protected compound was not the desired target, however, as it was found to be unsuitable for our planned synthesis; this material was made simply to confirm that the nitrile behaved in a similar manner to the aldehyde in the Diel-Alder reaction. In the next Section the alternatives to the ethylene ketal protecting group will be discussed.

Scheme 4.9

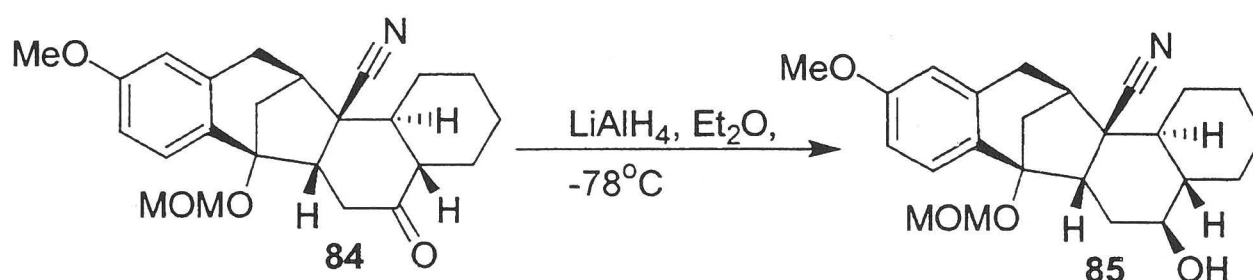


4.2 Improved protecting group strategy

As mentioned previously, the ethylene ketal was too labile for this synthesis so an alternative group had to be found. Rather than maintaining the oxidation state of the C5 carbon, it was decided that reduction to the alcohol would be a better option, as there is a much wider scope for the protection of alcohols than there is for the protection of ketones.

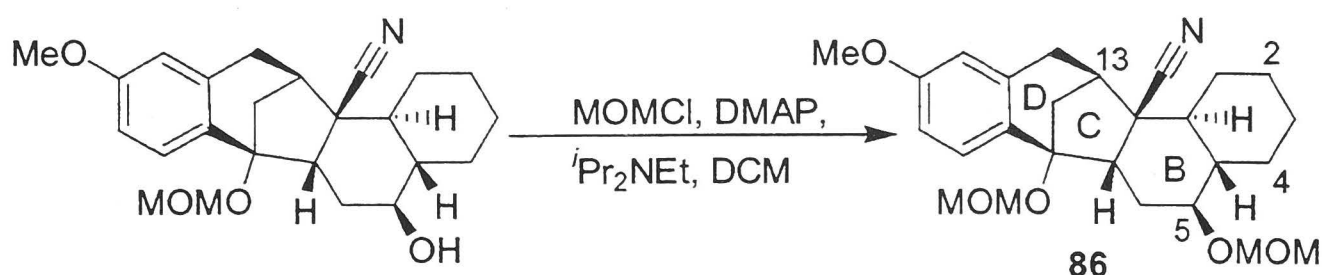
The use of NaBH_4 to reduce the ketone **84** gave a 1:1 mixture of diastereomers at C5. LiAlH_4 , however, was far more selective (Scheme 4.10), and gave a 10:1 mixture of epimers, favouring the isomer **85** with the hydroxyl *syn* to the nitrile function.

Scheme 4.10



The assignment of the C5 stereochemistry was based on 1D and 2D ^1H -NMR spectroscopic studies on the MOM protected alcohol **86**, which was easily synthesised using the standard conditions of MOMCl, DMAP and $i\text{Pr}_2\text{NEt}$ (Scheme 4.11).

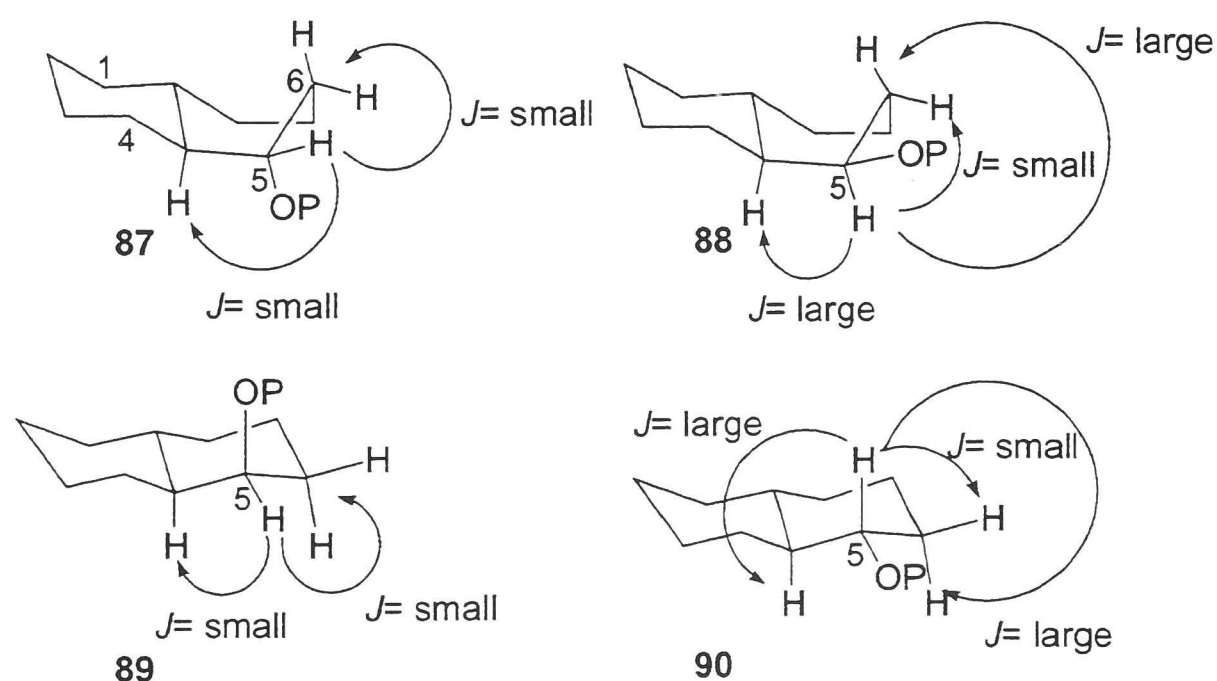
Scheme 4.11



The assignment of the stereochemistry at C5 could be deduced from two pieces of information obtainable from the ^1H -NMR spectra of the compound,

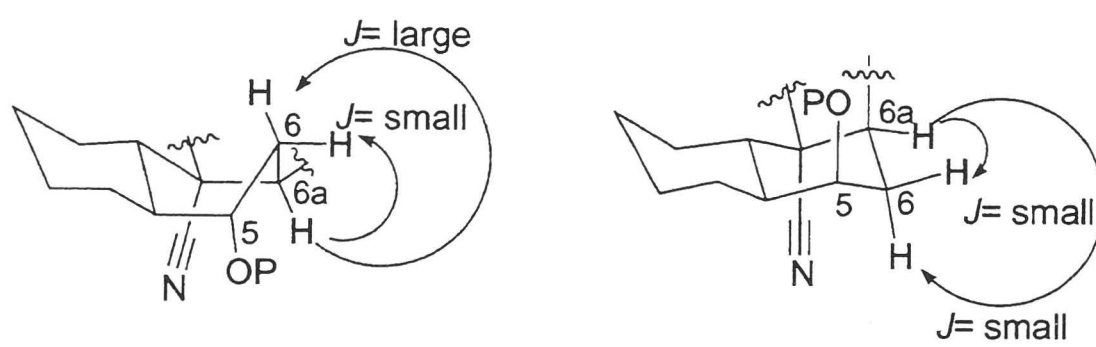
namely the conformation of the ring and whether the hydroxyl group was axial or equatorial (Figure 4.1). A 2D COSY ^1H -NMR spectroscopic study was performed to assign the hydrogens attached to the B-ring of the compound. From these data it was possible to deduce that the signal for hydrogen attached to C5 was at 3.57 ppm. This signal had no obvious splitting pattern, but the entire signal was no wider than 8 Hz, indicating several small couplings. This result is indicative of an equatorial hydrogen, as an axial hydrogen would show two large couplings to the two axial hydrogens at C4a and C6. Thus, the hydroxyl group is in the axial position and so structures 88 and 90 can be ruled out.

Figure 4.1



To distinguish between the boat and the chair conformation, the signal for the hydrogen attached to C6a was analysed (Figure 4.2). This signal came at 2.79 ppm and was a doublet of doublets (1H, $J=13.4$ Hz, $J=4.1$ Hz). This splitting pattern was consistent with the B ring taking up a boat conformation, as the chair conformation should give a triplet with two small coupling constants as indicated in Figure 4.2. From this analysis it is clear that the correct structure is 87, with the hydroxyl group is in the axial position, on the lower face of the molecule.

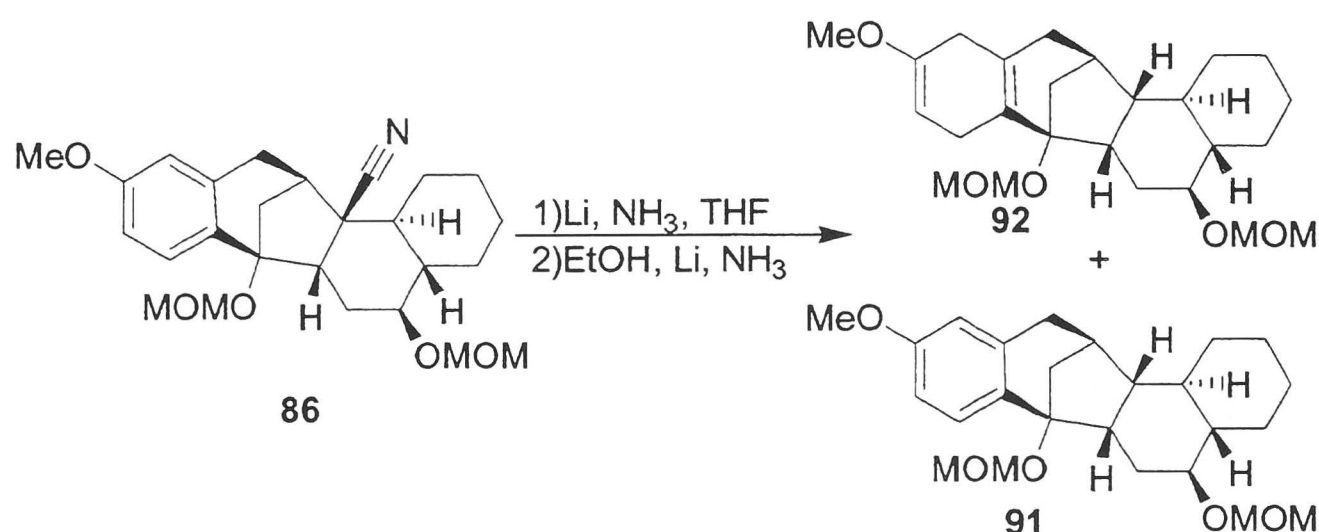
Figure 4.2



4.3 Birch reduction and enone formation

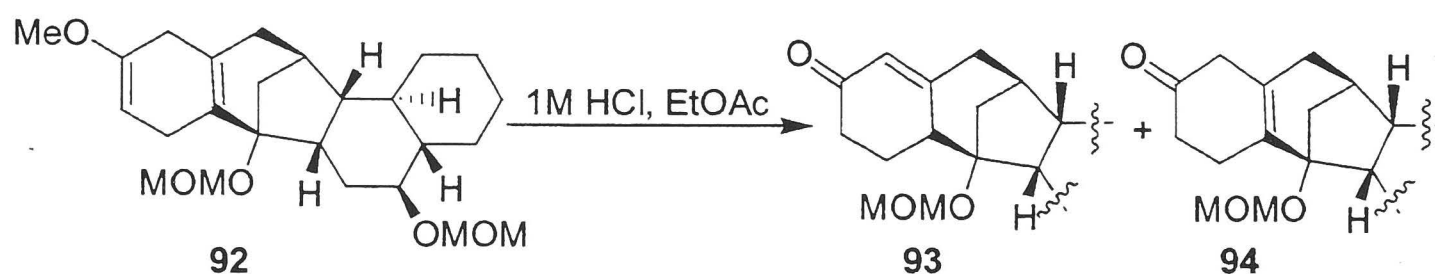
The decyanation of the *bis*-MOM ether **86** using dissolving metal conditions went smoothly, although attempts to reduce the aromatic ring in the same reaction vessel resulted in recovery of a large amount of the decyanated aromatic material **91**, as well as some of the Birch reduced product **92** (Scheme 4.14). This situation could be improved by increasing the ratio of THF to ammonia from 1:10 to 1:3, which had the effect of increasing the solubility of the intermediates.

Scheme 4.14



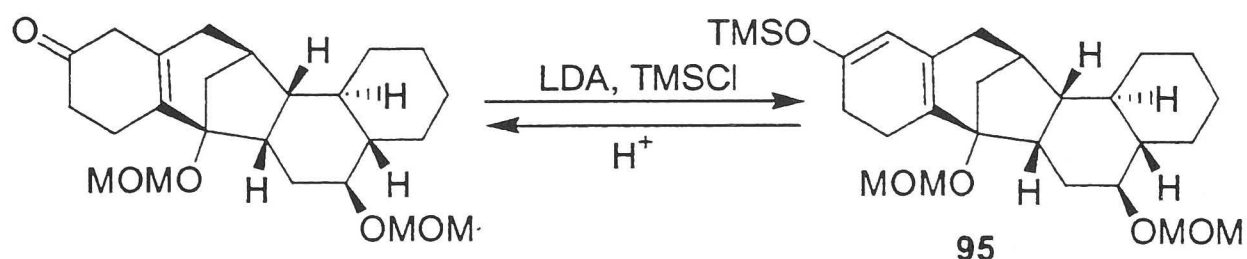
The hydrolysis of the methyl enol ether **92** and conjugation to the α,β -enone **93** was problematic (Scheme 4.15). Treatment of the crude Birch reduced material with 1 M HCl in ethyl acetate for 10 to 15 minutes gave a mixture of the α,β and β,γ -enones, with the β,γ -enone **94** predominating, although the ratio of the two products was highly variable, ranging from a 1:1 mixture to no α,β -enone at all. If the reaction was left to run for 12 hours or more an equilibrium mixture of 1:4 **93**: **94** was formed. Attempts to use ^tBuOK for the isomerisation of the β,γ -enone to α,β -enone were likewise unsuccessful.

Scheme 4.15



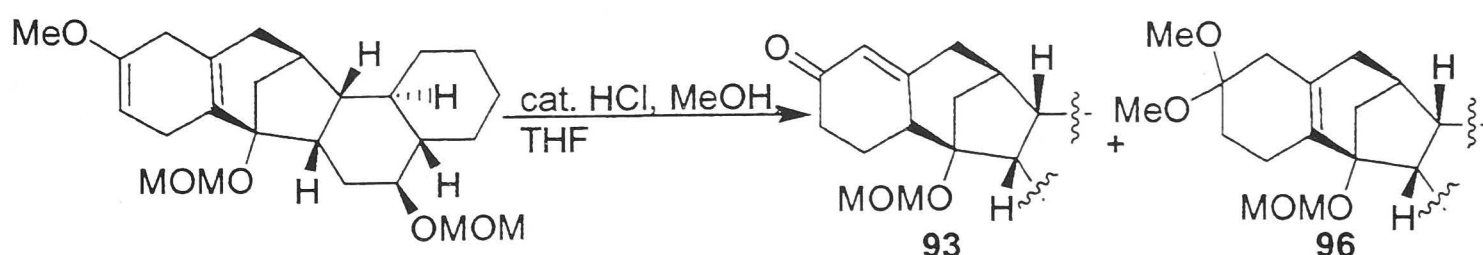
The conjugated silyl enol ether **95** was synthesised, in the hope that the system would protonate at the γ position, but this approach was also unsuccessful (Scheme 4.16). From these results it appeared that the β,γ -enone was the thermodynamic product and the α,β -enone would be difficult to obtain in any quantity.

Scheme 4.16



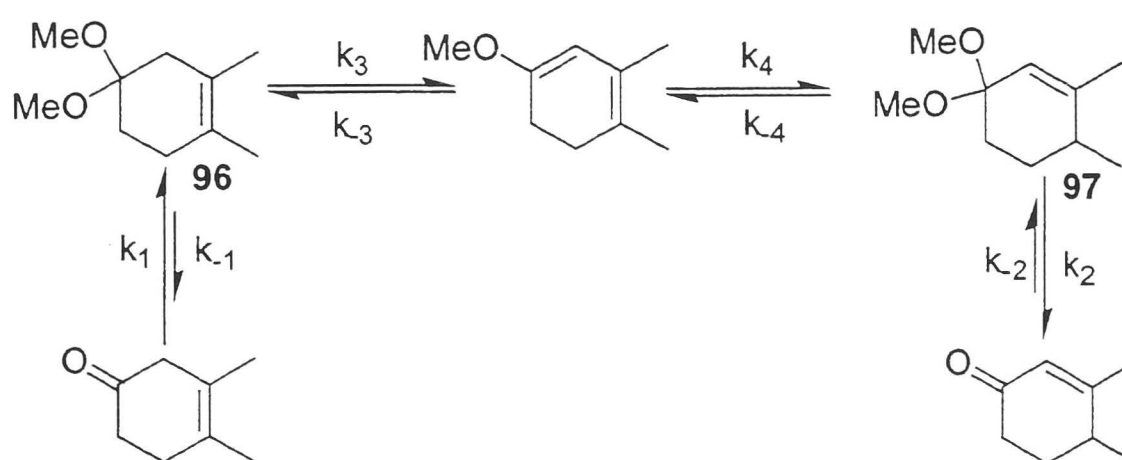
After much experimentation the solution to the problem was found to be the equilibration of the dimethyl acetal **96** with the α,β -enone **93** (Scheme 4.17). With this method the yield of the α,β -enone could be improved to 45-60% for the two steps from the nitrile. In addition, a 35% yield of a mixture of the dimethyl acetal **96** and the β,γ -enone **94** could be recovered after column chromatography of the reaction mixture. This material could be recycled to obtain an overall yield of 70-80% for the α,β -enone **93**.

Scheme 4.17

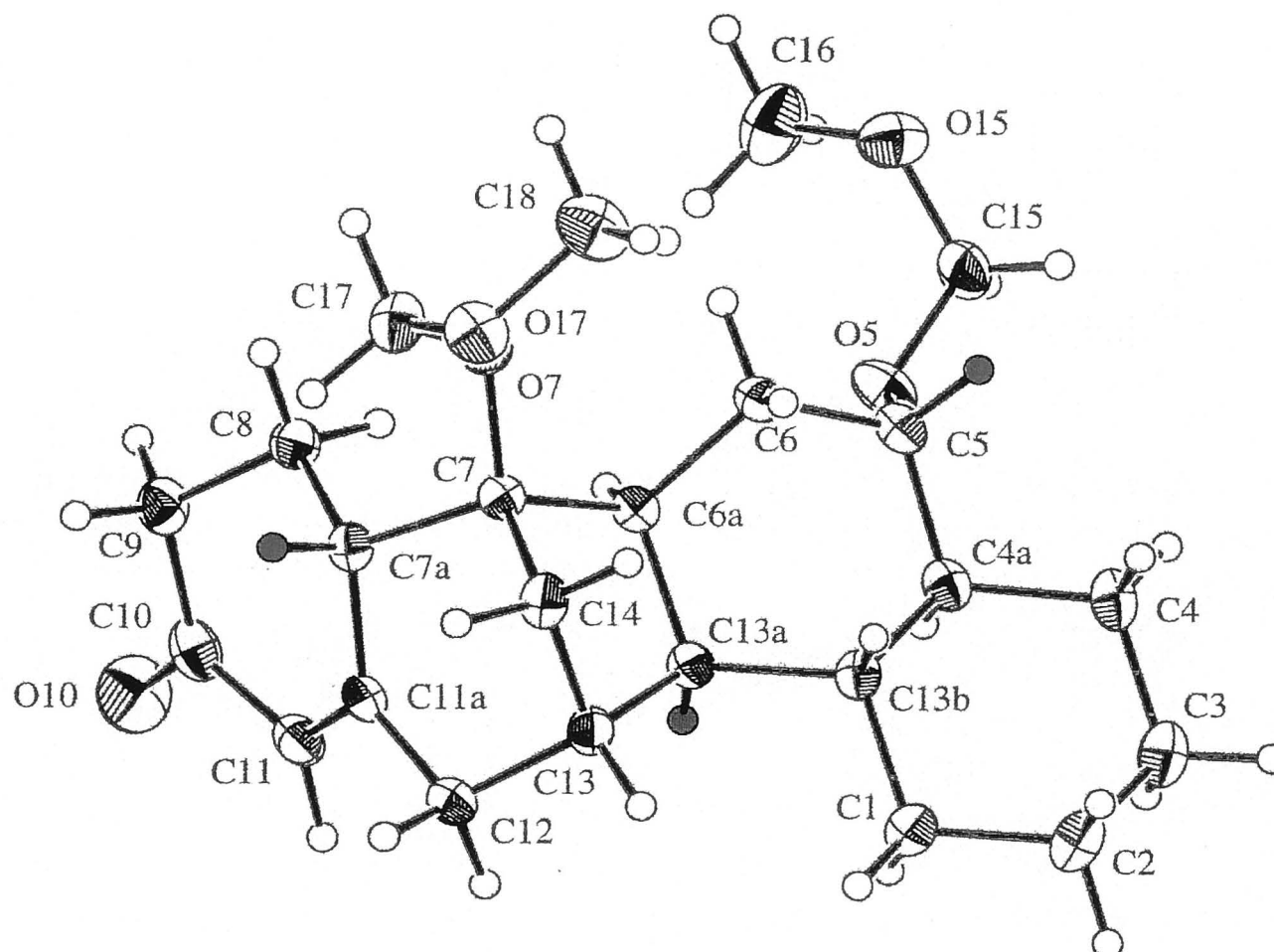


The equilibration works in this case, where it failed previously, for two reasons: dimethyl acetals form more readily from β,γ enones than from α,β enones, and the α -position of **96** is more acidic than the γ position of **97**. This sets up the equilibria shown below in Scheme 4.18. Comparing the relative rates of formation of the dimethyl acetals **96** and **97** from the corresponding enones, k_1 is faster than k_2 , while comparing the rate at which the common intermediate methyl enol ether forms, k_3 is faster than k_4 . This implies that the α,β -dimethyl acetal **97** forms faster than it is converted back to the β,γ -dimethyl acetal **96**. Since the interconversion of the dimethylacetals is faster than their formation ($k_2 < k_1 \ll k_3 \approx k_4$) the α,β -enone accumulates at a faster rate than the β,γ -enone.

Scheme 4.18



The α,β -enone **93** could be crystallised from ethyl acetate and petroleum spirit, allowing an X-ray crystal structure to be obtained. The ORTEP diagram is given in Figure 4.3. This ORTEP diagram allowed unambiguous assignment of the stereochemistry at C5, C7a and C13a (the hydrogens attached to these centres are coloured red). As can be seen from the ORTEP diagram, the oxygen substituent at C5 is on the lower face of the molecule, in the axial position, which confirms that the ^1H -NMR analysis performed earlier was correct in assigning this stereocenter.

Figure 4.3: The ORTEP diagram for compound 93 ⁵⁷

The proton attached to C7a is on the upper face of the molecule, which is the required stereochemistry for C7a as found in the target natural products. This stereochemistry was as expected, since the opposite stereochemistry would result in a highly disfavoured steric interaction between the hydrogens attached to C8 and C14.

Of much more importance was the stereochemistry of C13a. The hydrogen atom attached to this centre was unassigned in the ^1H -NMR spectra due to overlapping peaks in the aliphatic region, and hence no information on the stereochemistry of C13a was available from this source. The ORTEP diagram clearly shows that the cyano functionality was removed with retention of stereochemistry, as was expected from the discussion in Chapter 3, Section 3.

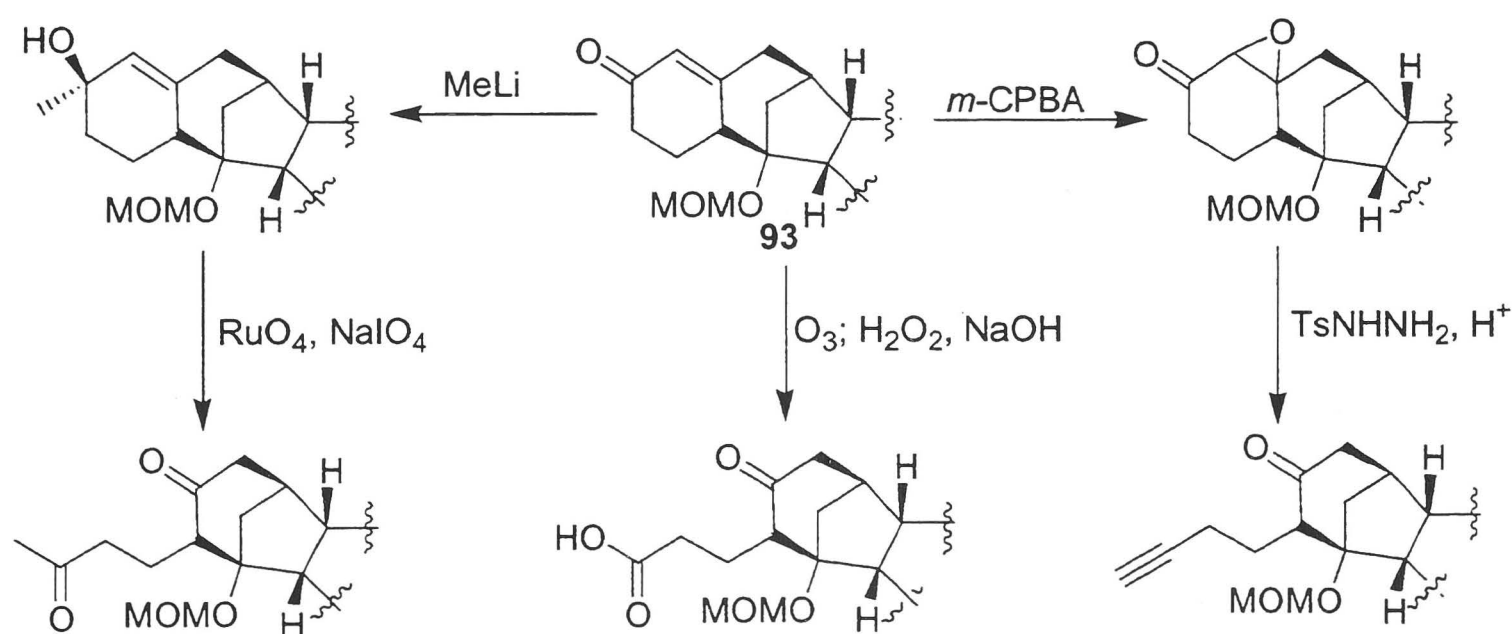
Chapter 5

Ring cleavage

5.1 Introduction to the ring cleavage

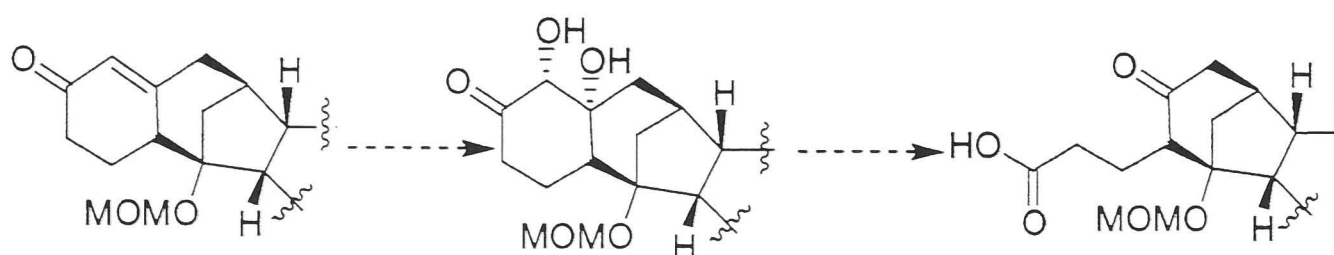
With the α,β -enone **93** in hand, the next transformation required was oxidative cleavage of the E-ring to give a compound suitable for formation of the piperidine ring found in the natural product. There were three different routes, as outlined in Scheme 5.1, which showed promise in achieving this goal. These sequences involved ozonolysis followed by basic peroxide, ruthenium tetroxide with sodium periodate co-oxidant and an Eschenmoser fragmentation.

Scheme 5.1



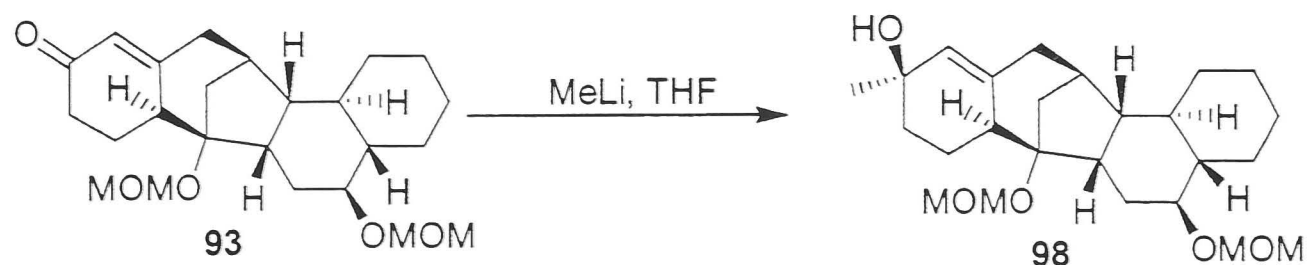
A fourth route, that proved to be unsuccessful, involved dihydroxylation of the double bond with osmium tetroxide, followed by sodium periodate cleavage (Scheme 5.2). Attempts to dihydroxylate the enone **93** using standard conditions⁵⁸ returned only starting material, even when heated to 100°C with pyridine.⁵⁹ It is well recognised that adjacent electron withdrawing groups deactivate double bonds toward dihydroxylation, so the double bond was activated toward OsO_4 by conversion to the allylic alcohol **98**, by using a 1,2-addition of methyl lithium to the enone (Scheme 5.3).

Scheme 5.2



It was found that this reaction gave the best results if the methyl lithium was added to the enone at -78°C , followed by warming rapidly to 0°C . Failure to follow this protocol resulted in a number of additional peaks in the alkene region of the ^1H NMR spectrum. The product was obtained as a 2:1 mixture of diastereomers, presumably with the major diastereomer being formed by attack of the methyl lithium on the less hindered lower face of the molecule.

Scheme 5.3

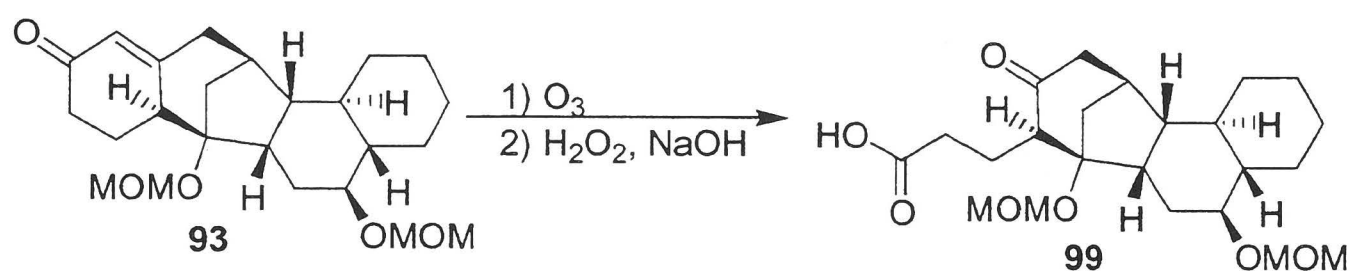


Unfortunately, this compound was also unreactive towards osmium tetroxide with either sodium periodate or *N*-methyl morpholine-*N*-oxide as co-oxidants. Attempts at heating the reaction mixture led to decomposition of the starting material.

5.2 Ozonolysis

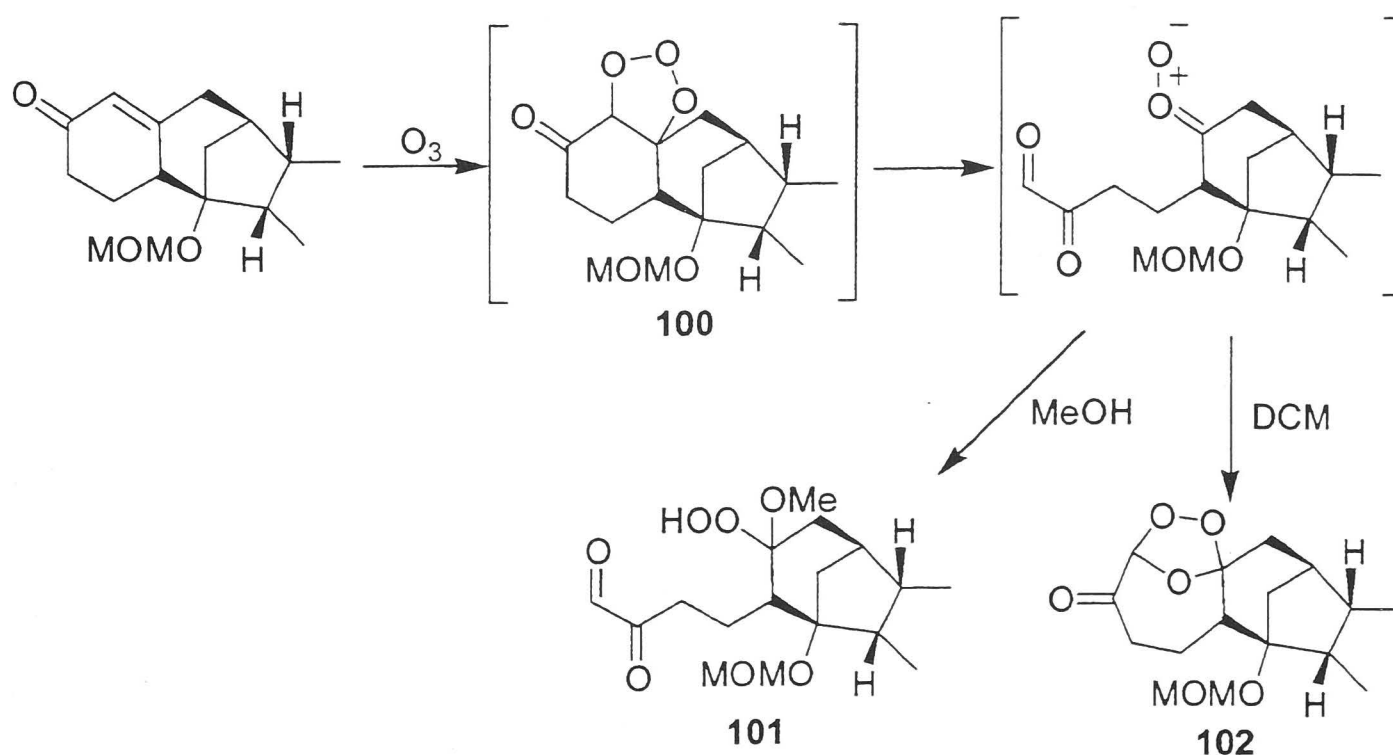
Ozonolysis followed by basic hydrogen peroxide is the oldest and most established method for the cleavage of enones with the product being a keto acid, such as compound **99** (Scheme 5.4).

Scheme 5.4



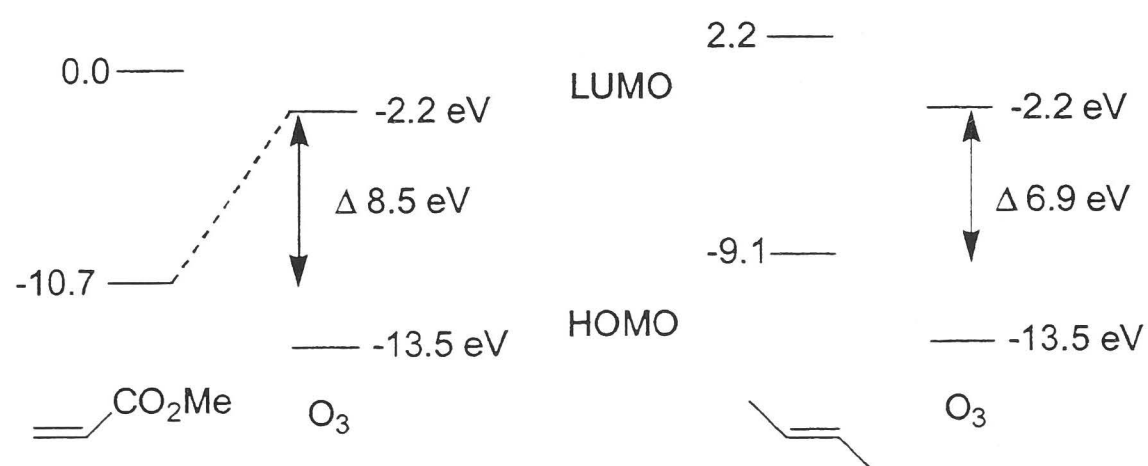
Ozonolysis is generally accepted to proceed through the Criegee mechanism,⁶⁰ the first step of which is the cycloaddition of ozone to the double bond to give a highly unstable primary 1,2,3-trioxolane **100** (Scheme 5.5). This intermediate rapidly rearranges to a ketone and a carbonyl oxide, with the carbonyl oxide forming on the more electron rich fragment. This product can have several fates, depending on the reaction conditions. The two most important final products are the α -methoxy hydroperoxide **101**, which is formed in methanol, and the 1,2,4-trioxolane **102**, which is formed in aprotic solvents.

Scheme 5.5



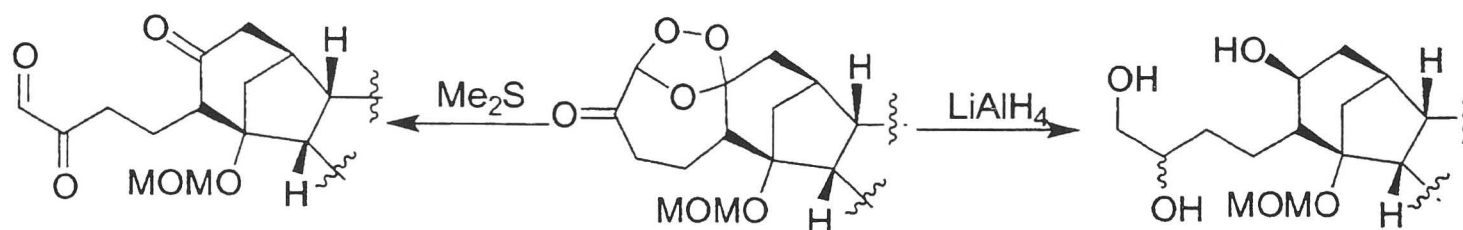
The substituents on the double bond affect the rate of reaction with ozone, with electron poor alkenes reacting more slowly than electron rich alkenes. According to FMO theory, ozone has a very low energy HOMO and LUMO, as is expected for a strong oxidant. As a result, the cycloaddition to an alkene is thought of as a reverse electron demand reaction, where the lowest energy interaction is between the LUMO of the ozone and the HOMO of the alkene. This results in a lower energy difference, and faster reaction with the higher energy HOMO orbital of electron rich alkenes, as shown in Scheme 5.6. An additional effect of the substituents on the double bond is steric, as highly hindered alkenes may react to form epoxides, rather than the usual 1,2,4-trioxolane when treated with ozone.

Scheme 5.6



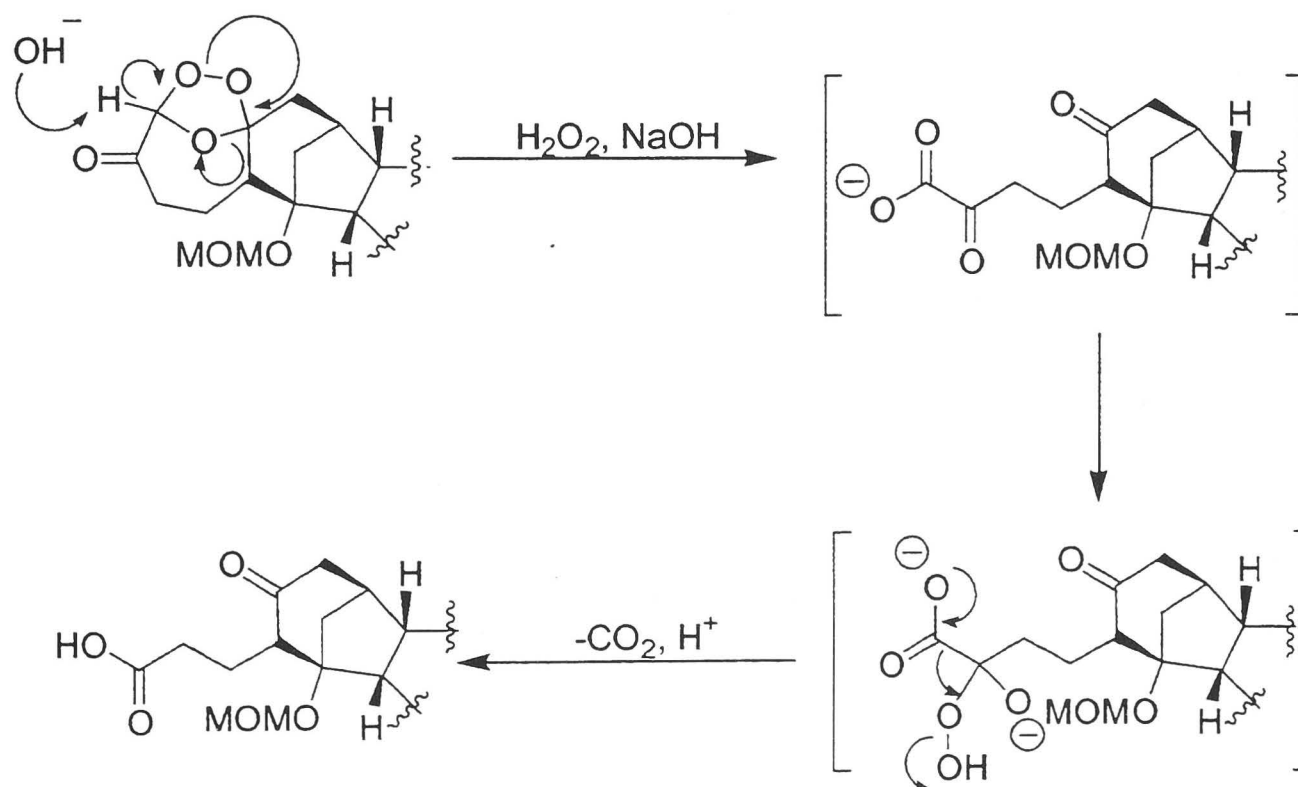
After ozonolysis, the products can be treated in a variety of ways to access a wide range of functional groups. Reduction with weak reductants such as dimethyl sulfide, zinc/acetic acid or any number of other reagents can lead to carbonyl compounds, while the use of strong reductants, such as lithium aluminum hydride or sodium borohydride can lead to alcohols (Scheme 5.7).

Scheme 5.7



A more desirable outcome for this synthesis could be achieved with the use of oxidative conditions for the workup of the 1,2,4-trioxolane, which leads to ketone and carboxylic acids as products (Scheme 5.8). Once again, there are a wide variety of oxidants that can be used, but the one most commonly used is basic hydrogen peroxide. In this instance, the initial product is an α -keto carboxylic acid, which can be oxidatively decarboxylated *in situ* to give a carboxylic acid with one carbon atom less than the starting material.

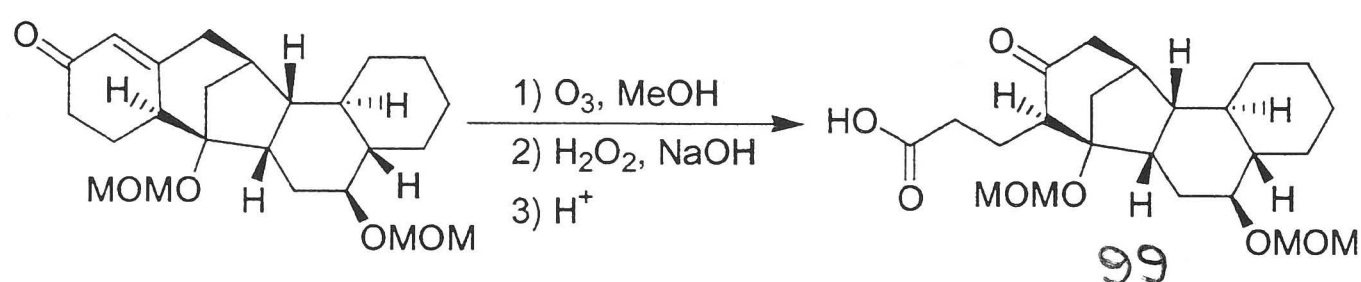
Scheme 5.8



The first attempts at ozonolysis of the enone **93** used dichloromethane as the solvent, but the yields improved significantly if the solvent was changed to methanol (Scheme 5.9). The ozonolysis was sluggish and required extended reaction times of up to 2 hours to consume all of the starting material. The intermediates from ozonolysis are known to be explosive, so they are rarely isolated; instead, the reaction was flushed with nitrogen to remove any

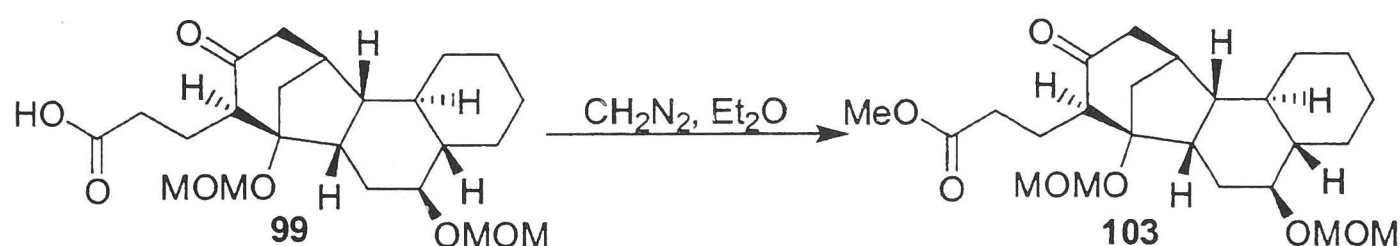
ozone and dilute sodium hydroxide and hydrogen peroxide were added to the solution. It was found that the best results were obtained when the hydrogen peroxide was added dropwise to the ice cold solution, no doubt due to the propensity for sodium hydroxide to decompose hydrogen peroxide rapidly at room temperature.

Scheme 5.9



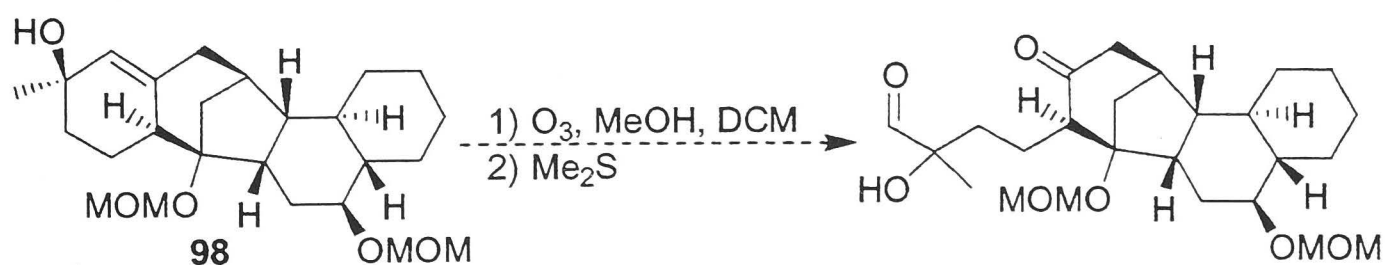
The carboxylic acid **99** obtained from this reaction was very polar, so to aid characterisation, the carboxylic acid was converted to the corresponding methyl ester **103** by treatment with diazomethane (Scheme 5.10). The overall yield from this reaction sequence was quite variable and ranged from 20 to 50%.

Scheme 5.10



An attempt was also made to cleave the tertiary allylic alcohol **98** with ozone (Scheme 5.11), but this process resulted in decomposition of the starting material, with no sign of any useful product.

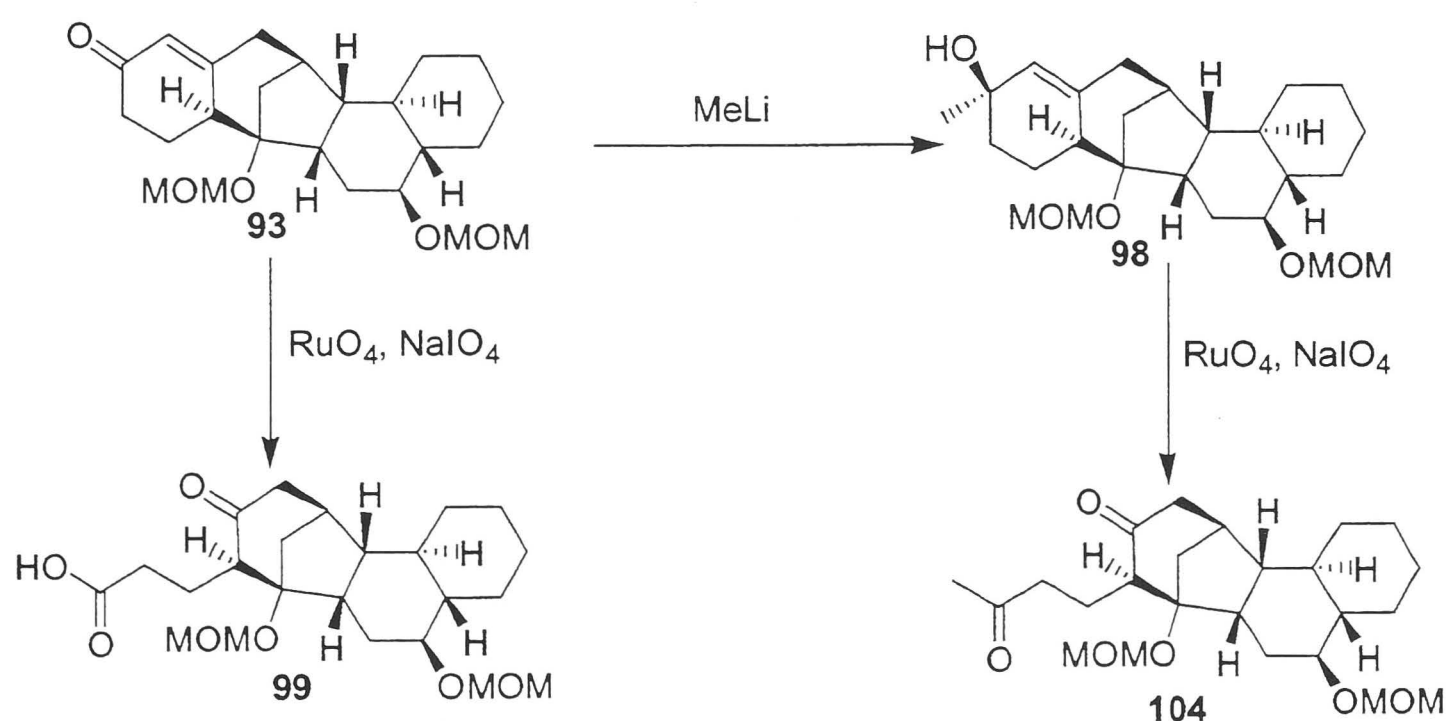
Scheme 5.11



5.3 Ruthenium tetroxide cleavage of compound 98

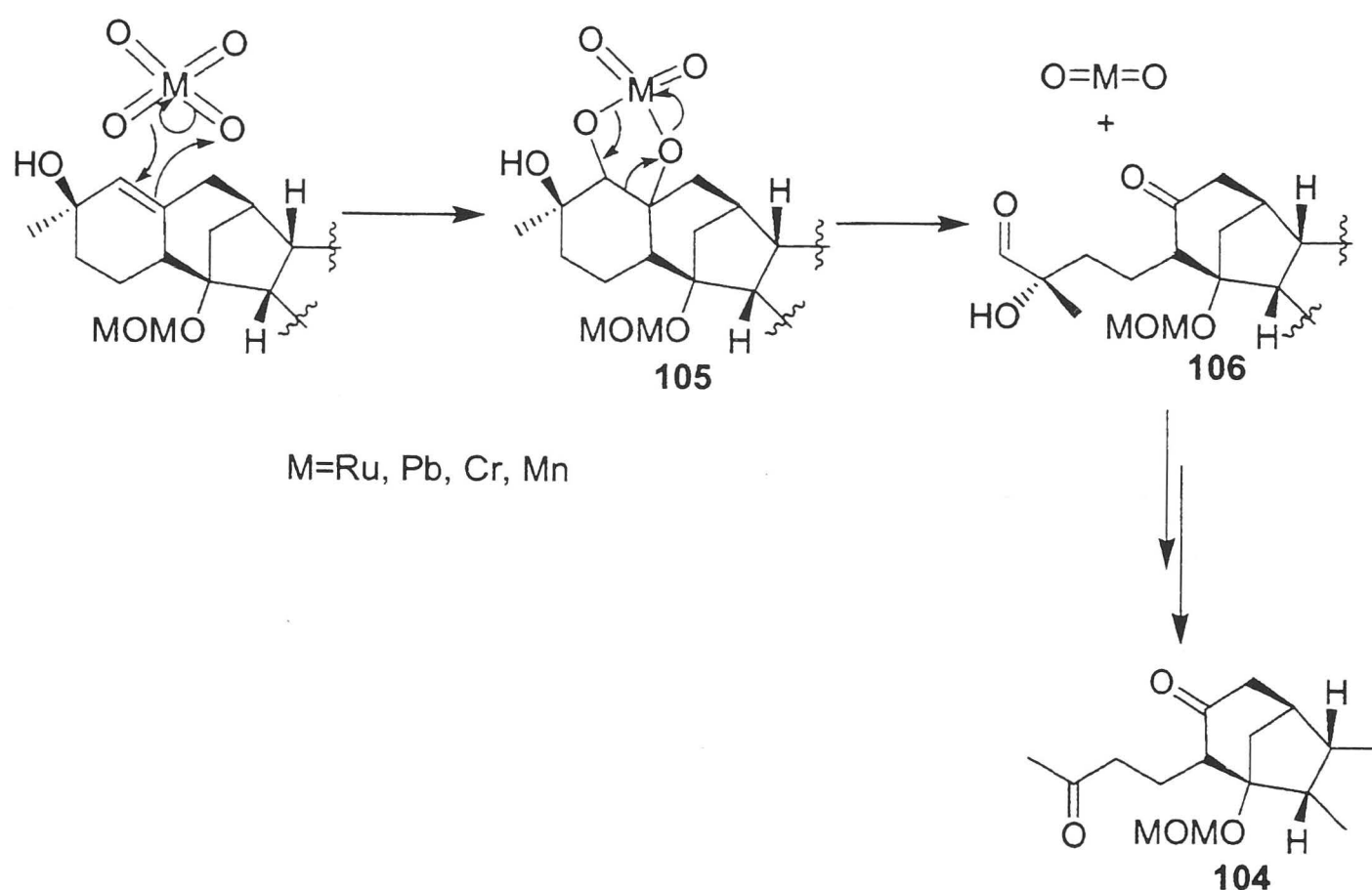
The second method we chose to explore for the cleavage of the ring was a ruthenium tetroxide catalysed reaction. Rather than attempting to cleave the enone, which would lead to the carboxylic acid **99**, which was available from ozonolysis, the allylic alcohol **98** was used instead, which would lead to the diketone product **104** (Scheme 5.12). This product has considerable potential and the two carbonyl groups should be sufficiently different to allow discrimination between them.

Scheme 5.12



There are a number of related oxidants that can also be used for this transformation, including acidic permanganate,⁶¹ acidic dichromate, and to a lesser extent, lead tetraacetate.⁶² All of these reagents, including ruthenium tetroxide, effect the cleavage through a similar mechanism, shown in Scheme 5.13, although lead tetraacetate requires the preformation of a diol to provide access to an intermediate similar to **105**. Once the ring is cleaved, the α -hydroxy aldehyde **106** can undergo further oxidative cleavage, or oxidation to the carboxylic acid, followed by oxidative decarboxylation to give the diketone **104**.

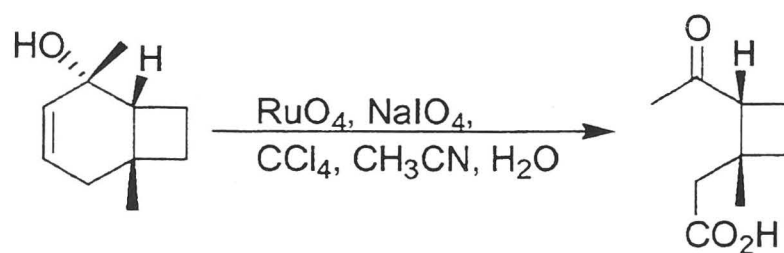
Scheme 5.13



The choice of ruthenium tetroxide for this transformation was dictated by the limitations of the other reagents. Both chromate and permanganate require acidic conditions to effect the cleavage, so would most likely result in loss of the MOM protecting groups. In addition, both are extremely powerful oxidants, capable of indiscriminant oxidation. Lead tetraacetate could also be ruled out as it had been shown previously that both the enone and the allylic alcohol were resistant to dihydroxylation.

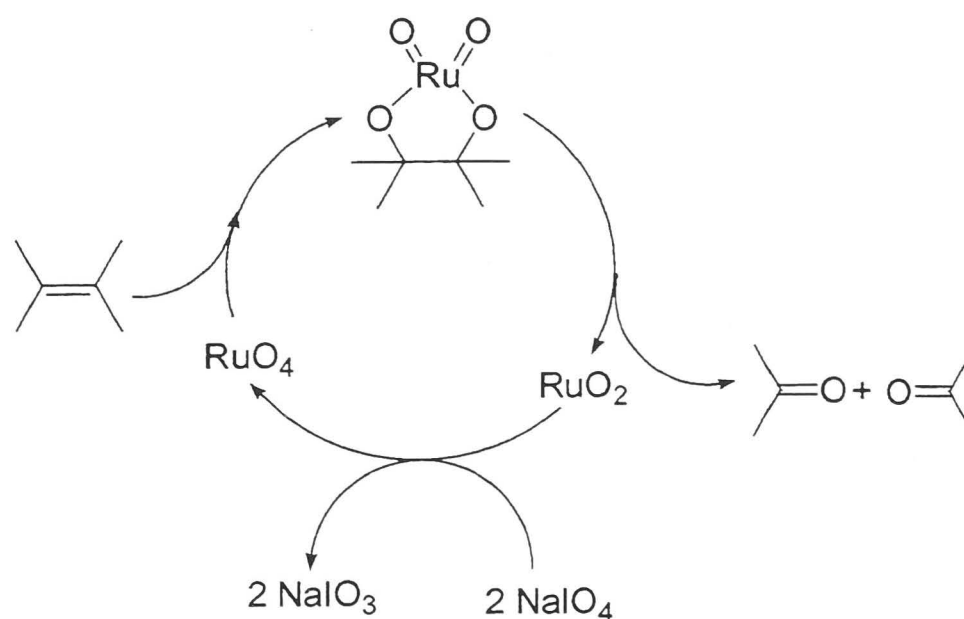
Traditionally, ruthenium tetroxide has been used in stoichiometric quantities, but this is expensive, and would only do half of the required transformation, leaving the α -hydroxy aldehyde to be cleaved in a second step. A more useful procedure, introduced in the early 1980's, uses a catalytic amount of ruthenium trichloride or ruthenium dioxide with sodium periodate co-oxidant.⁶³ An example of this reaction, which proceeded in 61% yield, is given in Scheme 5.14.⁶⁴ The reaction conditions are very mild, and did not result in any epimerisation of the stereocenter adjacent to the carbonyl function.

Scheme 5.14



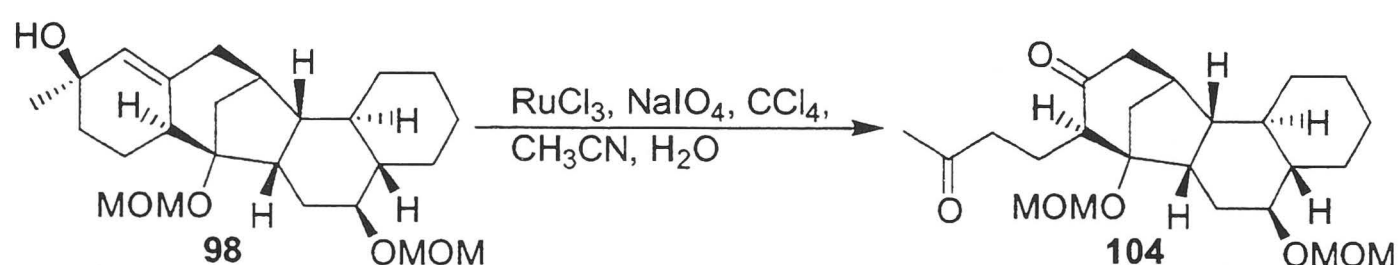
The catalytic cycle for this reaction is relatively simple, and is shown in Scheme 5.15. The reaction is usually carried out in a biphasic solvent system, consisting of water and carbon tetrachloride. In addition, acetonitrile is often used, particularly when an intermediate or a product is a carboxylic acid. The acetonitrile can coordinate preferentially to the ruthenium, preventing insoluble carboxylate complexes from forming, which would otherwise remove the catalyst from the cycle. The carbon tetrachloride is essential for rapid reaction to take place as the ruthenium tetroxide is soluble in this solvent, and so allows the oxidant to mix easily with the organic substrate to be oxidised. The water is also necessary, as most co-oxidants are water soluble, while the ruthenium dioxide formed in the reaction is insoluble in both phases. Accordingly, the reaction must be stirred vigorously to ensure turnover of the catalyst.

Scheme 5.15



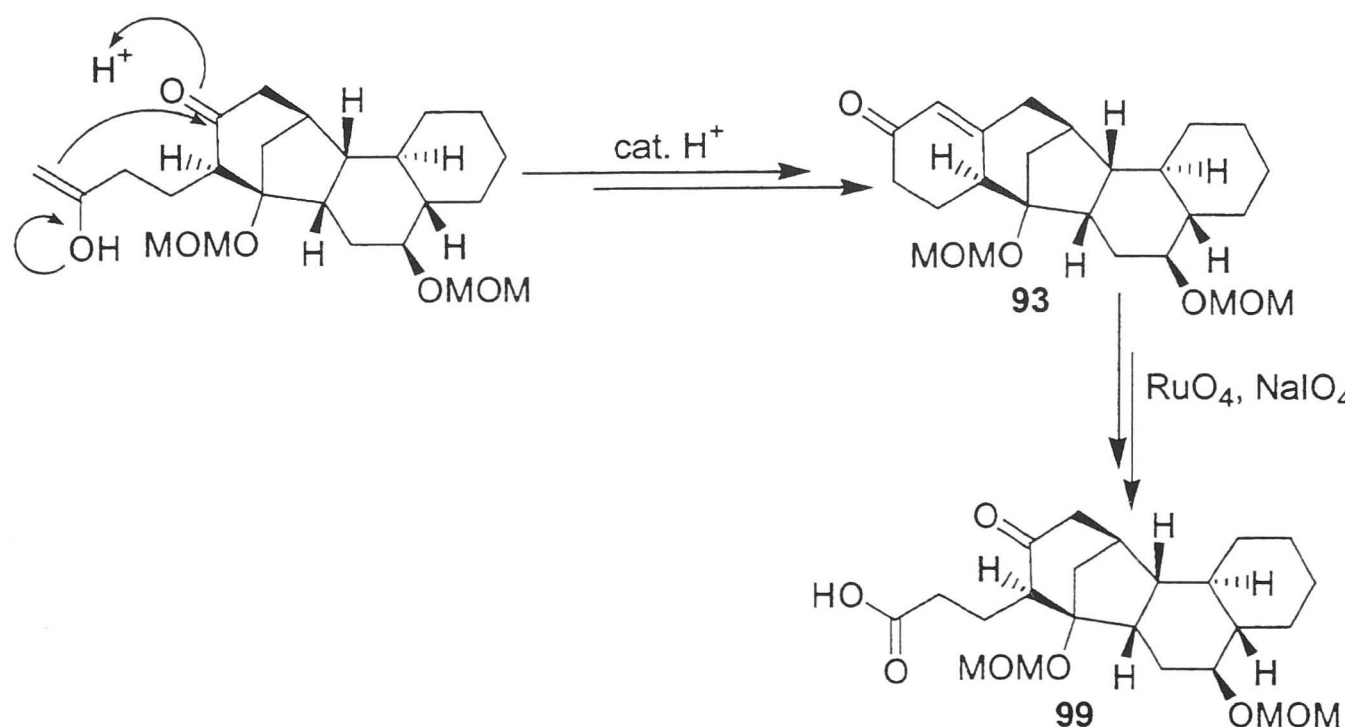
Treatment of the allylic alcohol **98** with ruthenium trichloride and sodium periodate in carbon tetrachloride, acetonitrile and water gave variable results (Scheme 5.16), with yields of the diketone **104** ranging from less than 10% to about 45%. In addition, the reaction was sluggish, and could take 24 hours for the starting material to be consumed.

Scheme 5.16



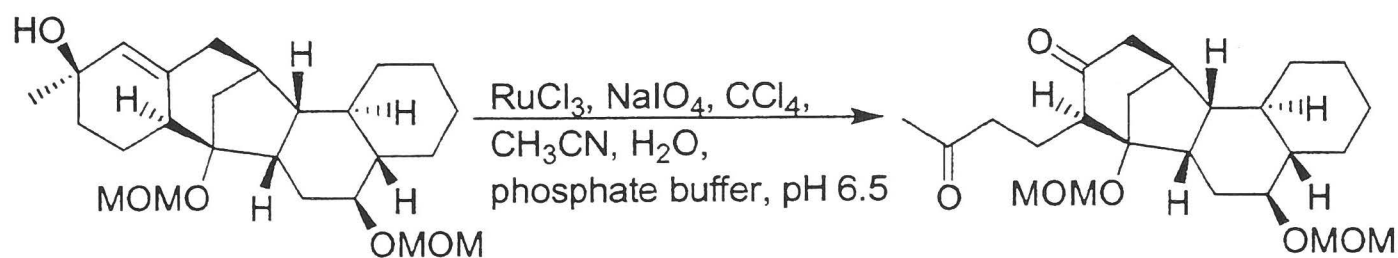
If the reaction was stopped before consumption of the starting material was complete, the ^1H NMR spectrum of the crude reaction mixture indicated that there was some enone **93** being formed. This led to the conclusion that the diketone product from the reaction was undergoing an aldol reaction to give the enone, which was in turn being cleaved to give the carboxylic acid **99**, thus slowing the reaction and lowering the yield (Scheme 5.17). The pH of the reaction was measured, and found to be below pH 2; this low pH had two sources, HCl liberated from the catalytic precursor and formic acid formed from the starting material.

Scheme 5.17



The first attempt to prevent this unwanted side reaction was to eliminate the HCl liberated from the catalytic precursor. This could be done by using ruthenium dioxide, or by preforming the catalyst with sodium periodate in water and extracting the ruthenium tetroxide formed into carbon tetrachloride. Both of these methods resulted in increased yields of the diketone to about 30-45%, but the reaction was still sluggish and the pH was still dropping to quite low levels as the reaction proceeded. The second method that was used was far more effective and involved using a phosphate buffer of pH 6.5, made from a 1:3 mixture of NaH_2PO_4 and Na_2HPO_4 (Scheme 5.18). With the phosphate buffer in the reaction, the consumption of starting material was complete within 3 hours, and the yield of the reaction was consistently above 40%.

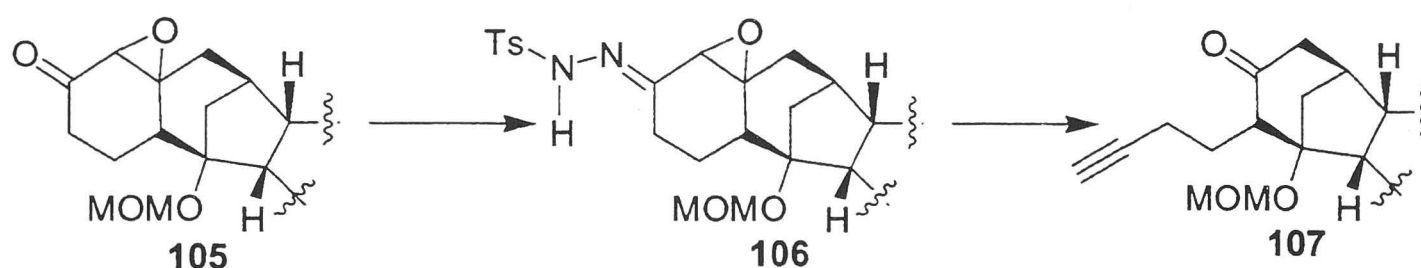
Scheme 5.18



5.4 Eschenmoser fragmentation: synthesis of the precursor

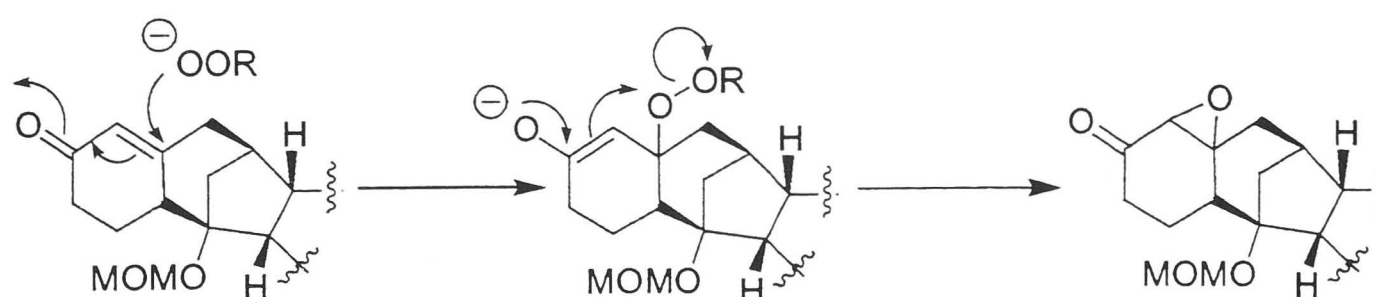
The Eschenmoser fragmentation is a powerful reaction that can cleave an enone to an alkynyl ketone, although an intermediate epoxy ketone must be synthesised first. Treatment of the epoxy ketone **105** with tosyl hydrazine would form the corresponding tosyl hydrazide **106**, which should then rearrange to the alkynyl ketone **107** (Scheme 5.19).

Scheme 5.19



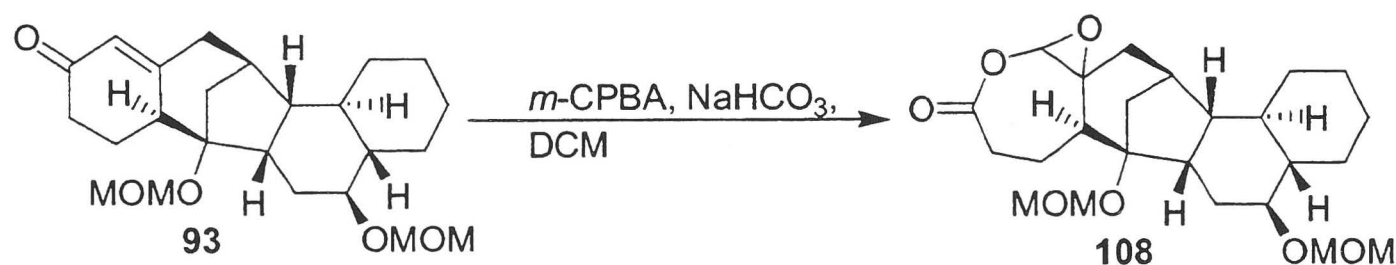
Before the Eschenmoser fragmentation could be carried out, an epoxy ketone must be formed first. There are a wide variety of methods available for the formation of epoxides from alkenes, but most are not suitable for electron deficient alkenes. The most common procedure for the synthesis of epoxides from enones is the use of a monoalkyl peroxide or hydrogen peroxide with a base.⁶⁵ The base deprotonates the peroxide, which can then undergo conjugate addition to the enone giving an enolate which can then displace alkoxide or hydroxide from the peroxide to give the epoxide (Scheme 5.20).

Scheme 5.20



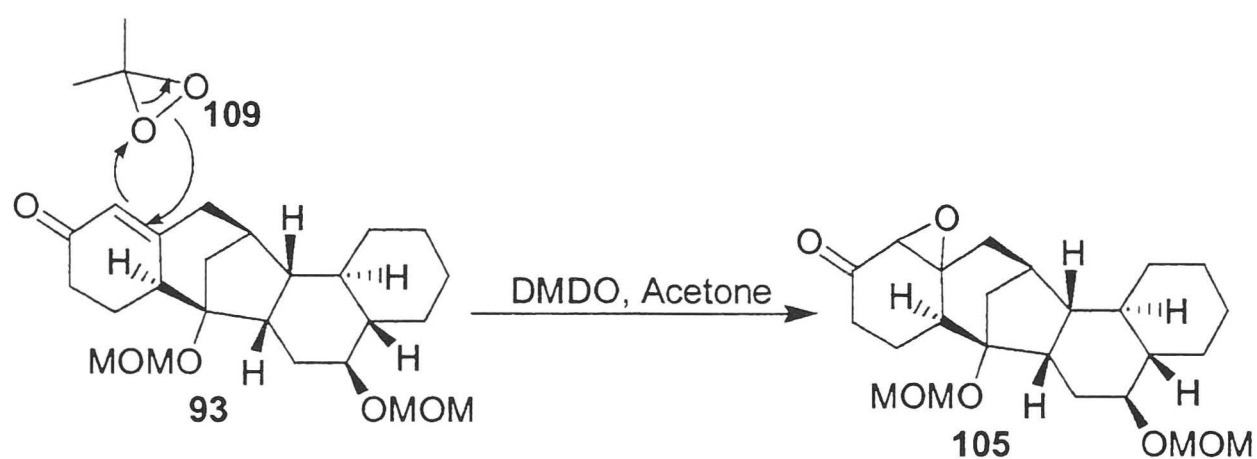
Unfortunately, the low reactivity of the double bond seen in the dihydroxylation earlier was also prevalent in this epoxidation reaction, as treatment of the enone **93** with either hydrogen peroxide/ sodium hydroxide or *tert*-butyl hydroperoxide with DBU or sodium hydroxide returned only starting material. Although it had been reported that treatment of enones with *m*-CPBA and a basic buffer could yield epoxy ketones,⁶⁶ an attempt to use these conditions for this synthesis did not result in the expected epoxy ketone, but the corresponding Baeyer-Villiger derived epoxide **108** instead (Scheme 5.21). This is unusual, as the Baeyer-Villiger reaction normally requires acidic conditions to proceed.

Scheme 5.21



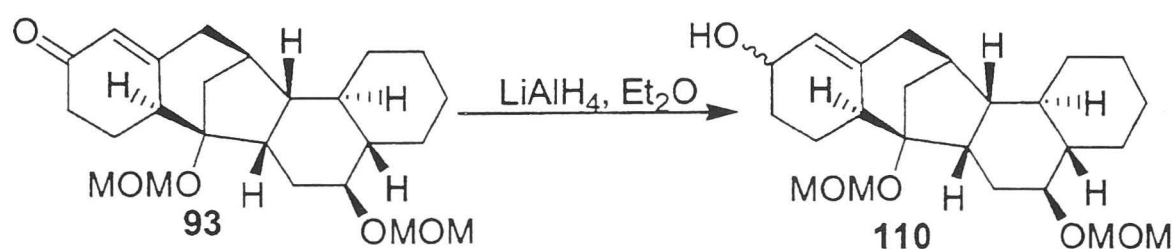
A third attempt to form this epoxide relied upon a recently introduced reagent, dimethyl dioxirane (DMDO, **109**), which is synthesised as needed from acetone and potassium hydrogen persulfate. This reagent has a unique mode of action compared with the other reagents available for epoxidation, involving a concerted oxygen transfer, and it has been reported to epoxidise many unreactive substrates. In the case of this synthesis however, this reagent gave only trace amounts of the epoxide **105** by ¹H NMR spectroscopy (Scheme 5.22). If the reaction was left for longer the starting material decomposed, while the more active trifluoromethyl methyl dioxirane also failed to give any quantity of epoxide.

Scheme 5.22



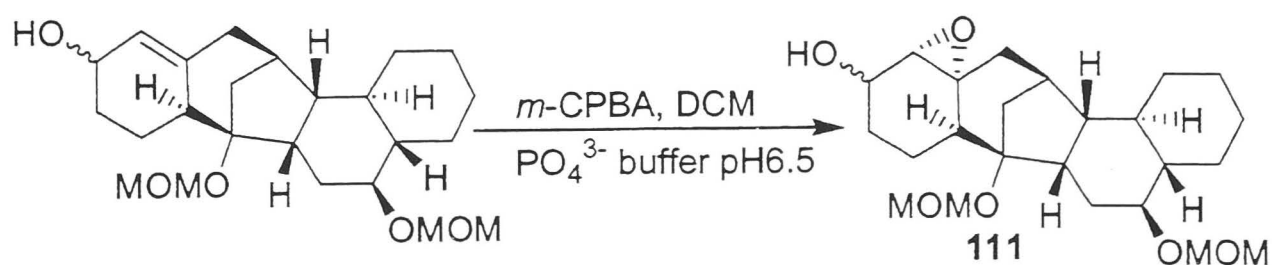
Since direct epoxidation of the enone was not proceeding as planned, the less expeditious route *via* the allylic alcohol **110** was explored. Treatment of the enone **93** with LiAlH_4 at 0°C cleanly gave the allylic alcohol as a 5:1 mixture of diastereoisomers as the sole products by ^1H NMR spectroscopy (Scheme 5.23).

Scheme 5.23



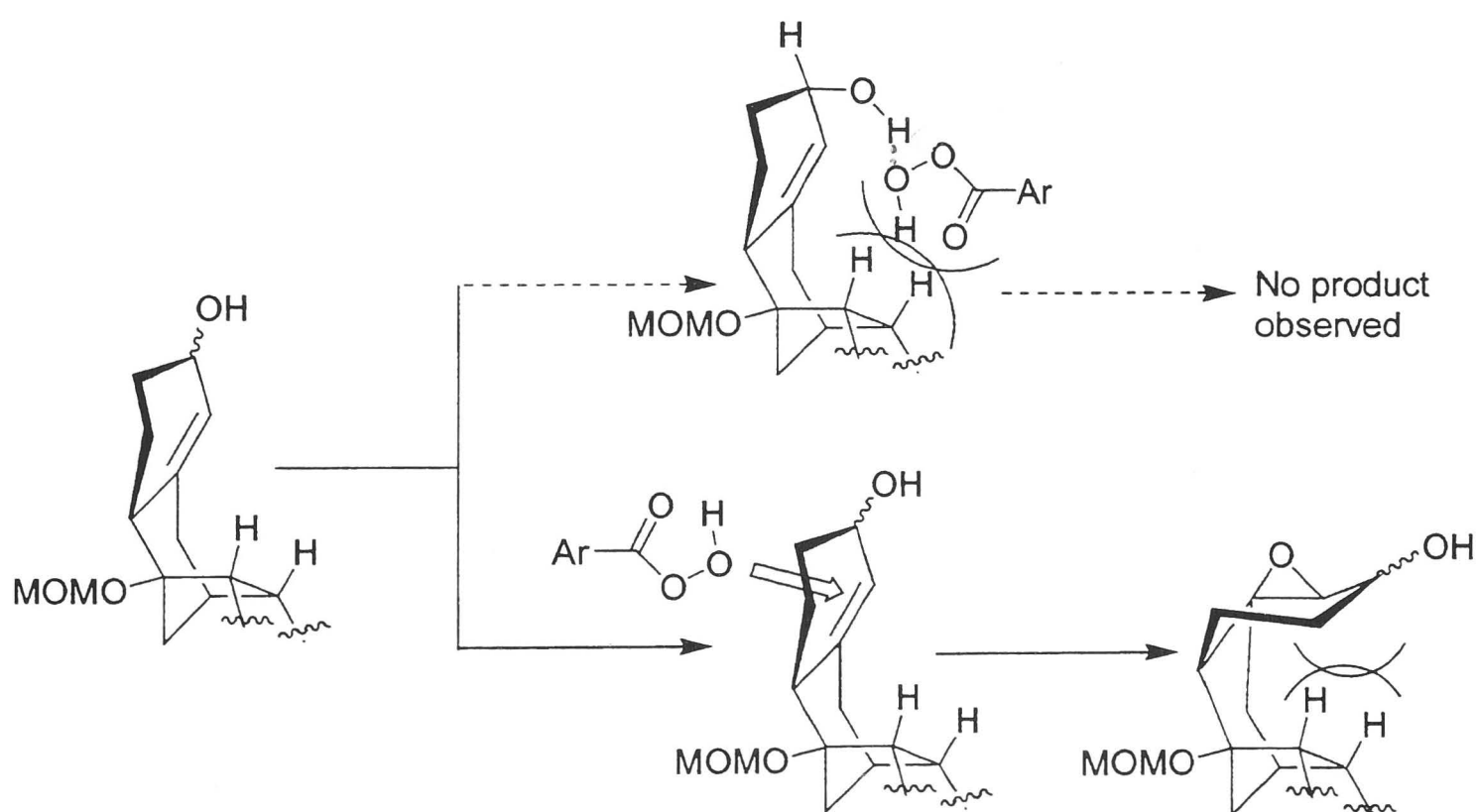
The stereochemistry of the major isomer was not proven, as ultimately this feature would have no relevance to the synthesis. Treatment of the allylic alcohol with *m*-CPBA and a phosphate buffer of pH 6.5 then gave the epoxy alcohol **111**, again in high yield, and as a mixture of two diastereomers (Scheme 5.24).

Scheme 5.24



The absence of the other two possible diastereomers from the ^1H NMR spectrum was not surprising, as the reagent should only approach from the less hindered bottom face of the compound to give just one of the two epoxide diastereomers (Scheme 5.25), even though in the case of the minor isomer this is contrary to the expected stereochemistry based on the well known directive effects of allylic alcohols with *m*-CPBA. As can be seen from the 3D representation of the product, conversion of the sp^2 centre at C11a to an sp^3 centre results in severe steric buttressing between C11 and the two carbon bridge of the bicyclooctane ring system. This is clearly one of the causes of the low reactivity for the C11-C11a double bond.

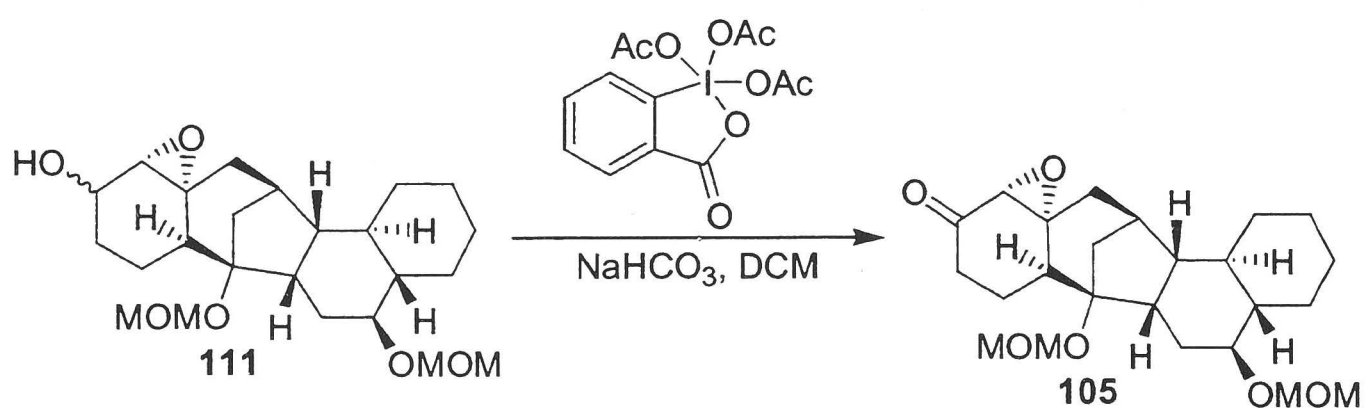
Scheme 5.25



With the epoxy alcohol 111 in hand, all that was needed to obtain the Eschenmoser precursor was to oxidise the alcohol to the ketone. The choice of reagent at this point was very limited, as the oxidant must be neither acidic nor nucleophilic, as the epoxide might not survive the reaction conditions. Dess-Martin periodinane is well known for its mildness and high selectivity, although it is very difficult to obtain the reagent without traces of

acetic acid present. However, the acetic acid can be neutralised by the addition of sodium bicarbonate to the reaction mixture. Treatment of the alcohol **111** with Dess-Martin periodinane and sodium bicarbonate cleanly gave the epoxy ketone **105** as a single diastereomer (Scheme 5.26). Purification of this material by column chromatography gave a 77% overall yield of the epoxy ketone **105**, for the three steps from the enone **93**.

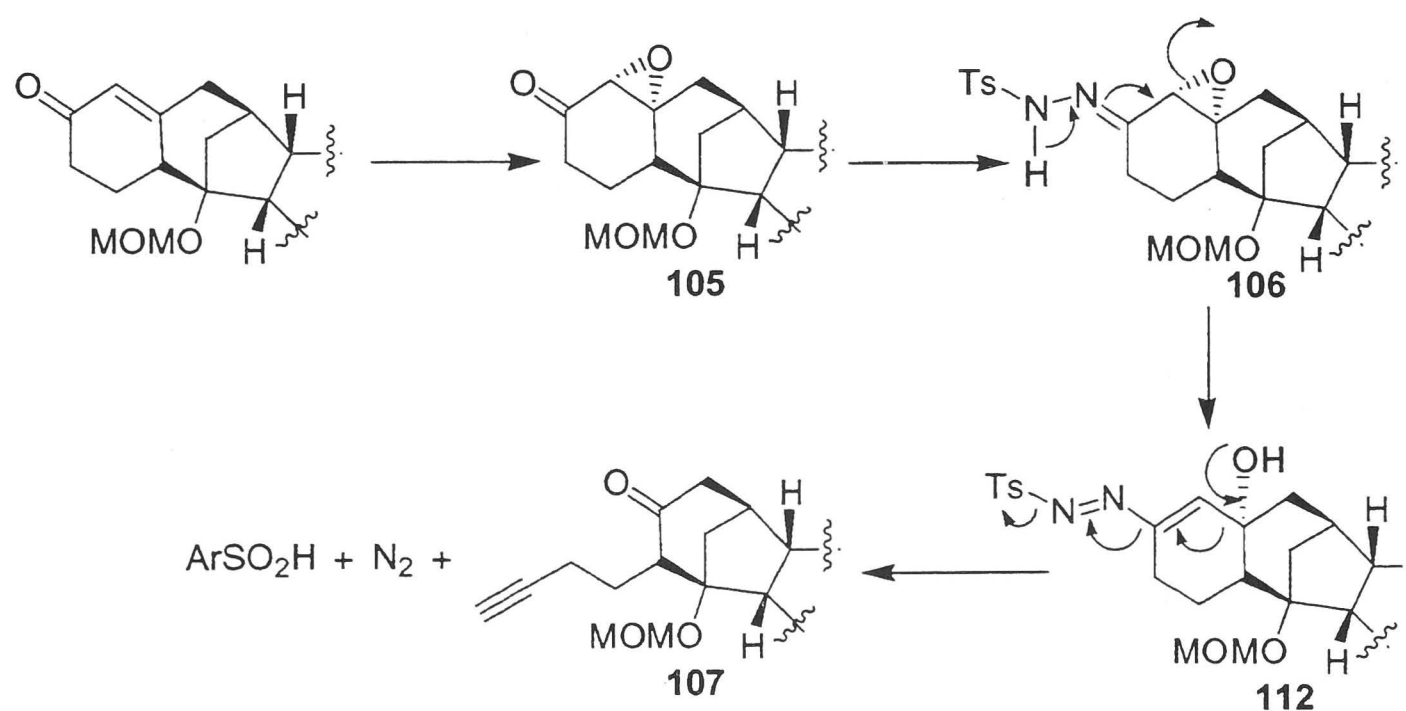
Scheme 5.26



5.5 The Eschenmoser fragmentation

With the epoxy ketone **105** finally synthesised it was time to explore the Eschenmoser fragmentation. The Eschenmoser fragmentation is initiated by treatment of an epoxy ketone with tosyl hydrazine, to form the corresponding hydrazone **106**. The hydrazone can then open the epoxide as shown in Scheme 5.27 to give an intermediate of the type **112**. A lone pair of electrons on the oxygen then initiates fragmentation of the ring to the alkynyl ketone **107**, with loss of nitrogen and toluenesulfinic acid.⁶⁷

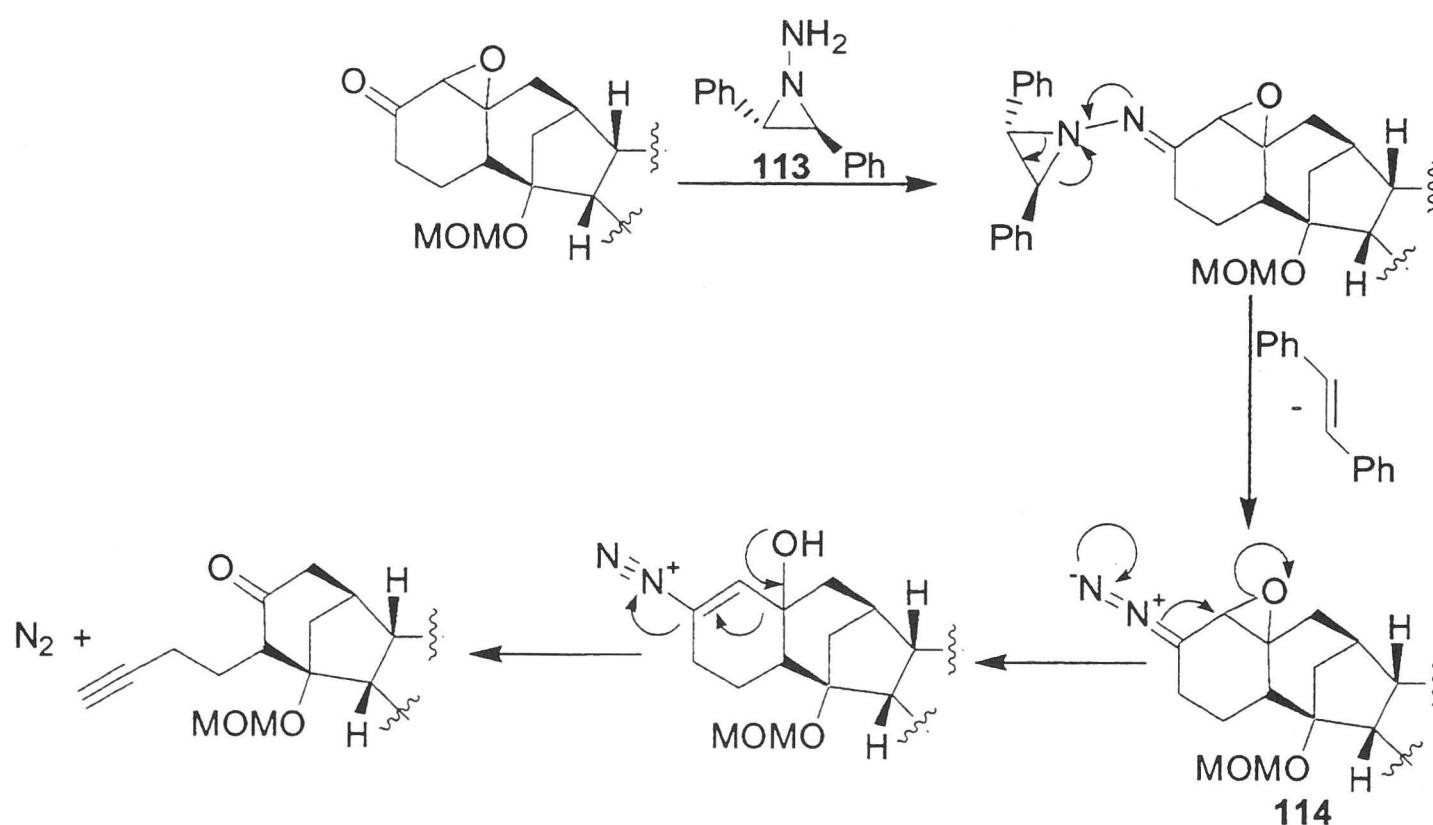
Scheme 5.27



There are a number of variables that can be manipulated with the Eschenmoser fragmentation, including the hydrazine substituent, the catalyst and the solvent. The most common hydrazine used for the Eschenmoser fragmentation is tosyl hydrazine, but the intermediate tosyl diimine **112** can require forcing conditions to convert to the alkynyl ketone. The use of 2,4-dinitrobenzenesulfonyl hydrazine can enhance the rate of this final step in the fragmentation as the nitro groups help to stabilise the sulfinyl anion leaving group. Another variation on the Eschenmoser fragmentation is the use of *N*-aminoaziridine reagents such as the diphenyl

substituted reagent **113**. While this reagent can give superior results it is not available commercially and so has not found widespread use. The mechanism for the fragmentation with *N*-aminoaziridine reagents is slightly different to that of the hydrazine reagents, and involves an epoxy diazoalkane intermediate **114**, as shown in Scheme 5.28.

Scheme 5.28

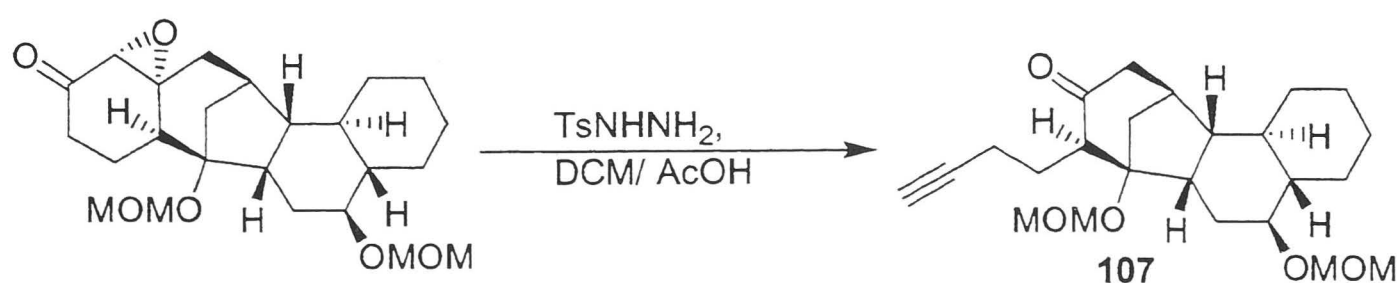


The catalysts for these reactions are many and varied, and can be acidic, such as acetic acid or silica gel, or basic, such as sodium methoxide, pyridine or carbonate. Acetic acid was the earliest catalyst, and was often used as a co-solvent with DCM. The large excess of acetic acid used can cause problems, especially if the compounds are acid sensitive. Although silica gel is far milder than acetic acid, the reaction can still attain high levels of acidity, as the by-product from the reaction is a sulfinic acid. Because a sulfinic acid is formed in the reaction, the reaction can also proceed without any added catalyst, as the sulfinic acid is acidic enough to catalyse the reaction. The use of base catalysed Eschenmoser fragmentations is far less common and is often associated with the use of 2,4-dinitrobenzenesulfonyl hydrazine.

The solvent can be polar, such as methanol or ethanol, or the solvent can also serve as the catalyst, such as acetic acid. Non polar solvents such as dichloromethane or THF have also been used. The polar solvents can stabilise the ionic intermediates best, and are the most common solvents. In particular, acetic acid/ DCM in a 1:1 ratio is very common. When silica gel is used as a catalyst the preferred solvents are non polar as the alcoholic solvents can dissolve the silica gel.

The use of a 1:1 ratio of acetic acid and DCM to effect the Eschenmoser fragmentation gave variable yields of the alkynyl ketone **107**, ranging from 10-40% (Scheme 5.29). A significant amount of the material recovered from this reaction was a polar yellow compound that appeared to be the intermediate tosyl diimine **112**, by ^1H -NMR spectroscopy. Attempts to leave the reaction longer were complicated by loss of the MOM protecting groups. When the catalyst was changed to silica gel the reaction again returned the yellow intermediate as the major product, and both heating and longer reaction times resulted in loss of the MOM groups.

Scheme 5.29

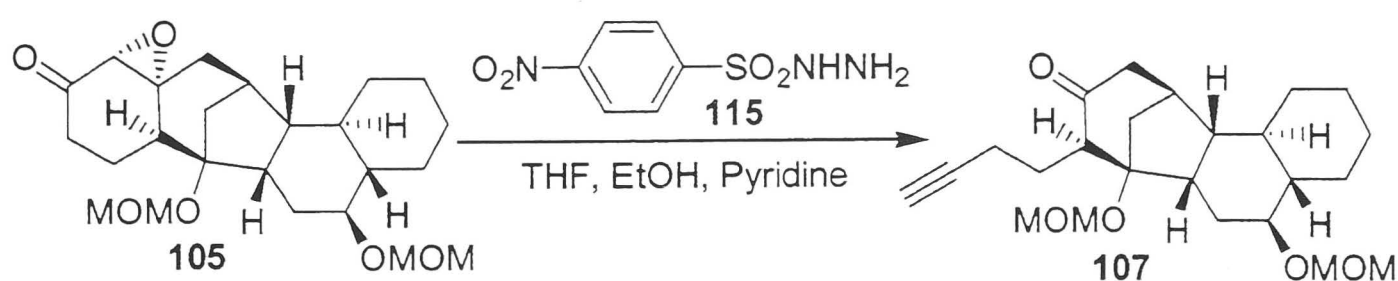


4Å Molecular sieves were explored as an alternative dehydrating reagent, and after two days at room temperature there was no sign of the yellow intermediate by TLC, although the isolated yield was still poor, at about 40%. The use of sodium methoxide was explored next, and once again the yield from the reaction was poor. It was observed that the yellow colour from the intermediate was quenched upon addition of the sodium methoxide, but the colour reappeared on the TLC plate. If this reaction was

stirred overnight, all of the intermediate was consumed by TLC, but the yield was again very low at less than 40%.

Attempts to synthesis 2,4-dinitrobenzenesulfonyl hydrazine were not effective, and the reagent could not be synthesised in high purity, due to the high ambient temperature causing partial decomposition of this very unstable compound. An alternative was 4-nitrobenzenesulfonyl hydrazine (115), which is stable below 40°C, and could be made in quantitative yield from 4-nitrobenzenesulfonyl chloride and 98% hydrazine. 4-Nitrobenzenesulfonyl hydrazine (115) is insoluble in most solvents except THF. Treatment of the epoxy ketone 105 with this reagent in THF gave a very slow reaction, so it was found that the addition of ethanol to the reaction mixture was necessary to enhance the rate. In addition, pyridine was added to the reaction to reduce the acidity. This reagent combination gave a 76% yield of the alkynyl ketone 107 (Scheme 5.30).

Scheme 5.30



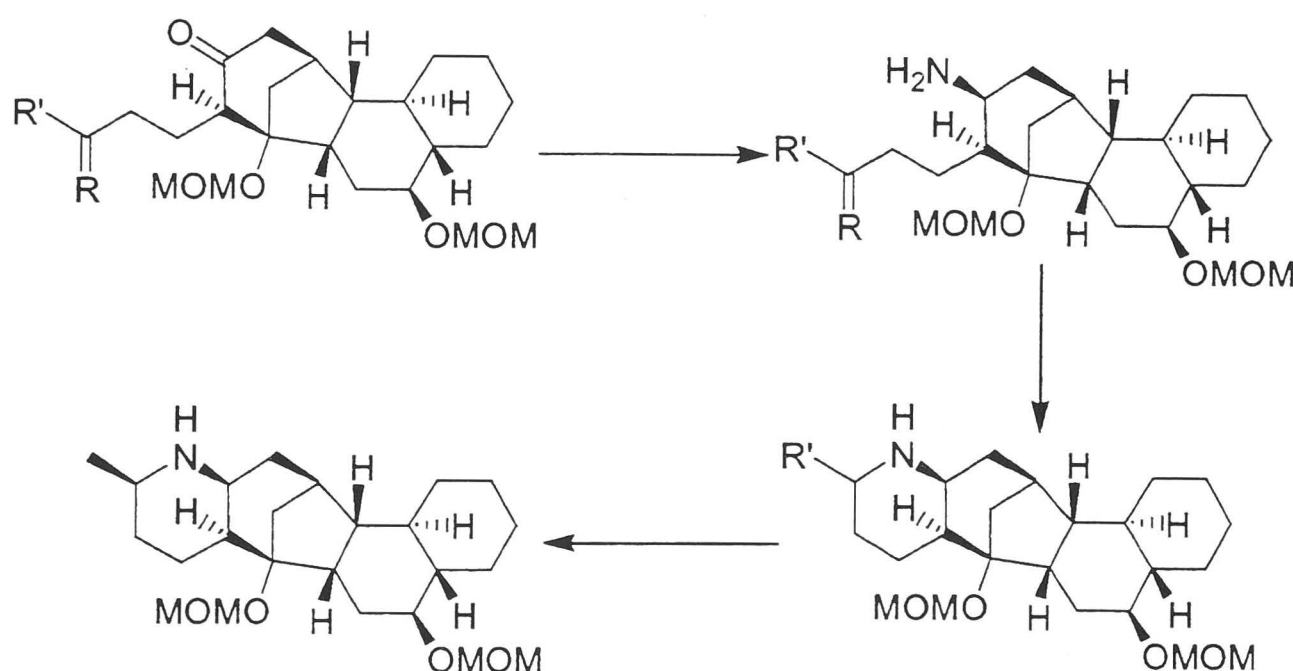
Chapter 6

Synthesis of amino derivatives

6.1 Attempted reductive amination

In the previous chapter, several methods for the synthesis of keto compounds were discussed. The general plan for this synthesis involved reductive amination of these ketones, followed by cyclisation onto the side chain to generate the piperidine ring (Scheme 6.1).

Scheme 6.1

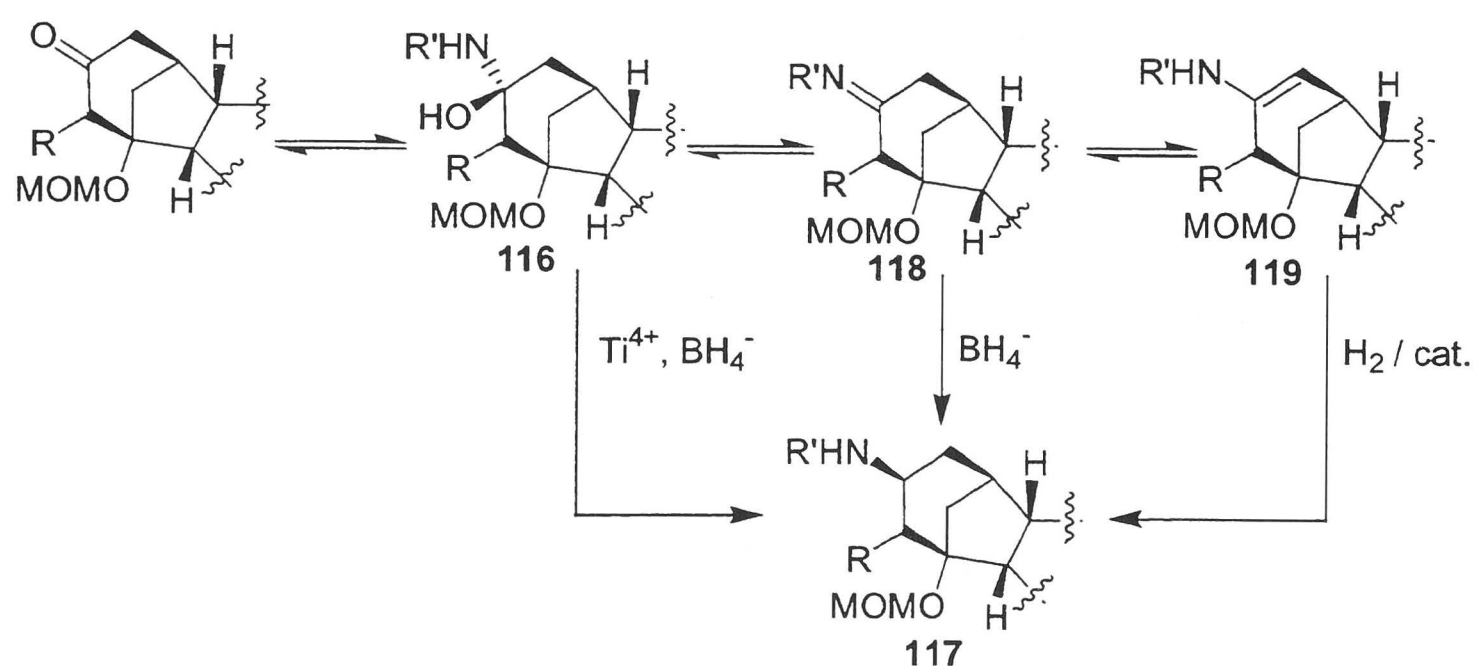


There are a large number of examples of the reductive amination of ketones in the literature, and there are numerous methods and reagents available for this transformation.⁶⁸ While a thorough discussion of this reaction is beyond the scope of this thesis, the general mechanism for the reductive amination of ketones remains the same regardless of method, as discussed below.

First, a nucleophilic nitrogen species attacks the ketone to form an intermediate α -amino alcohol **116**, which can have several fates, depending upon the structure of the ketone and the reaction conditions. This α -amino alcohol can be reduced directly to the amine **117** in a few rare cases to give the amine directly, but more usually the α -amino alcohol dehydrates to give an imine **118**, usually under mildly acidic conditions, or an enamine **119**

under basic conditions. The imine or the enamine can then be reduced, either *in situ* or following isolation (Scheme 6.2). It must be noted that all of the steps up to the reduction are in equilibrium, so methods that favour the shifting of the equilibrium to the right will enhance the rate at which the amine will be formed.

Scheme 6.2



The choice of the nitrogen source is wide, and can be ammonia, a primary or a secondary amine. In addition, the nitrogen source may be used as the free amine or as the ammonium salt. The choice of ammonium salt versus free amine, and the reducing agents used will determine the pH of the reaction, and this can have a large effect on the success of the reductive amination.

The pH of the reaction has such a pronounced effect on the outcome since a low pH will favour the imine (i.e. **118**) over the enamine (i.e. **119**), but will protonate the nitrogen source used, thus decreasing or totally masking the nucleophilicity of the nitrogen, thereby inhibiting or preventing the formation of the α -amino alcohol. The ratio of imine to enamine is also important, as different reducing agents react with the two species with greatly different rates.

The most common reducing agents for the reductive amination of ketones are the borohydride family of reagents, and to a lesser degree, aluminum hydrides. In particular, sodium cyanoborohydride is very common because under the mildly acidic conditions that favour imine formation, sodium cyanoborohydride will not reduce ketones, thus allowing a simple one-pot procedure. Borohydride and aluminum hydride reagents will not react readily with enamines so the reductive amination conditions must favour the imine species. This factor often precludes the use of aluminum hydrides, as their high basicity can often deprotonate the imine to form the enamine.

The second class of reducing agents used for reductive aminations is the transition metal catalysed hydrogenation. Although these reagents can reduce the enamine species, their use is much less common, as the amines formed can poison the metal catalyst, and there is no selectivity for the intermediate imine species over the ketone, thus requiring complete formation and isolation of the imine before reduction.

In addition to the necessary reducing agent and nitrogen source, additives can also be used in the reductive amination to enhance the reaction. The additives fall into two categories: Lewis acids that promote nucleophilic attack on the ketone and enhance the rate of reduction; and dehydrating reagents, which drive the equilibrium towards formation of the imine species. The most common Lewis acids used are titanium tetraisopropoxide, titanium tetrachloride and zinc halides. The dehydrating agents can be added into the reaction, such as titanium tetrachloride or they can be external, such as molecular sieves in a soxhlet apparatus or the use of a Dean-Stark apparatus. As in the case of titanium tetrachloride, the additive used can have both Lewis acidic and dehydrating capabilities.

Many attempts were made at a reductive amination of the ketones **103**, **104** and **107**. The results are presented in Table 6.1 below. None of the reactions

were successful, but in several instances small amounts of new substances were observed in the ^1H -NMR. Unfortunately, attempts to increase the yield of these products were unfruitful and attempts to isolate these new compounds by standard column chromatography were similarly unsuccessful. Once again, the low reactivity of the sp^2 centre at C9 appeared to be preventing the desired reaction from taking place.

Scheme 6.3

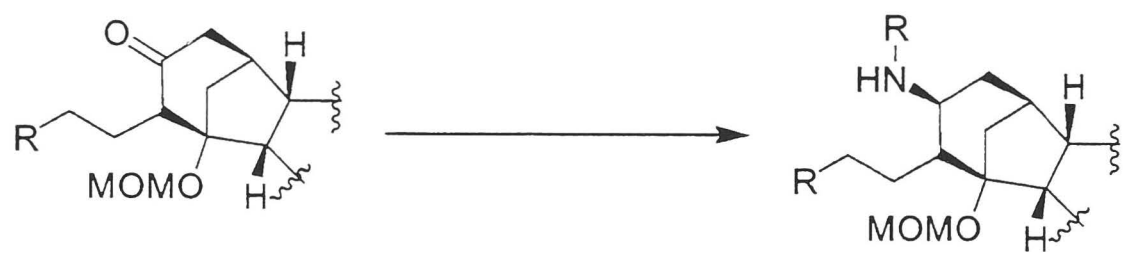


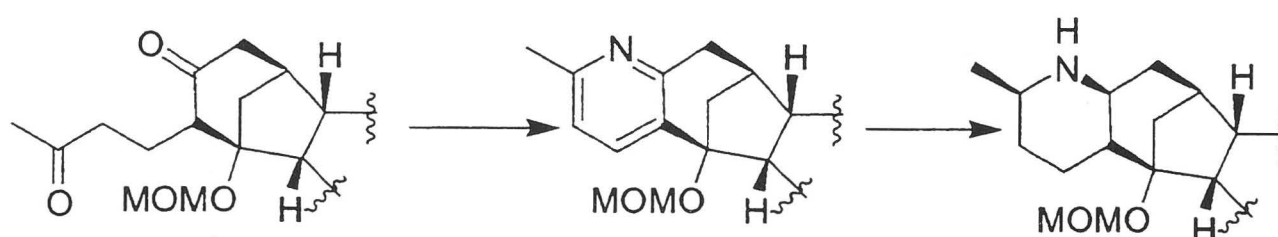
Table 6.1: Attempted reductive amination of the C9 ketone

	Starting material	Amine source	Reductant	conditions	Product
1	Ester 103	NH ₄ OAc	NaBH ₃ CN	EtOH, r.t.	Trace
2	Ester 103	NH ₄ OAc; NH ₄ Cl	NaBH ₃ CN	Ti(O ⁱ Pr) ₄ , THF /EtOH, r.t.	None
3	Ester 103	NH ₄ Cl	NaBH ₃ CN	THF /EtOH, reflux	None
4	Ester 103	BnNH ₂	NaBH ₃ CN	TiCl ₄ ,Toluene reflux	Decomp.
5	Diketone 104	BnNH ₂		P ₂ O ₅ , THF	Decomp.
6	Diketone 104	BnNHTMS .HCl	NaBH ₃ CN	THF	Trace
7	Alkyne 107	BnNHTMS .HCl	NaBH ₃ CN	THF	None
8	Alkyne 107	NH ₄ OAc	NaHB(OAc) ₃	NEt ₃ , THF	None
9	Alkyne 107	BnNH ₂	NaBH ₃ CN	Neat, 100°C	Trace

6.2 Pyridine formation and attempted reduction

Since the reductive amination of the C9 ketone was unsuccessful, a new route was devised that involved formation of a pyridine, followed by reduction using catalytic hydrogenation (Scheme 6.4).

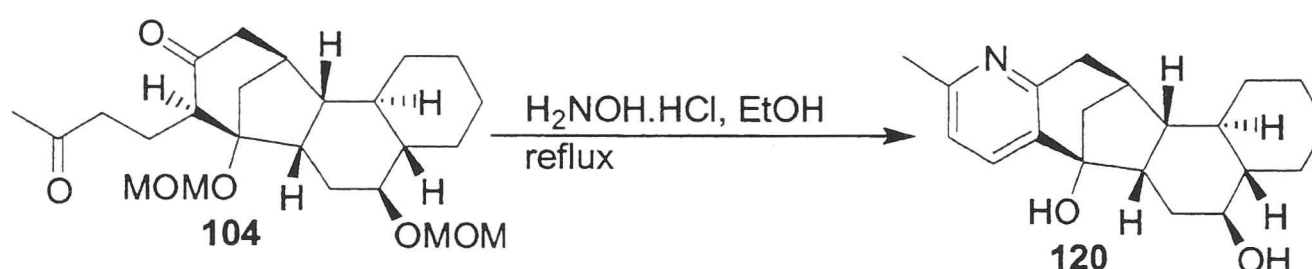
Scheme 6.4



The conversion of 1,5-diketones to pyridine compounds is well-established, and is reasonably straight forward, as the pyridine compound represents a thermodynamic sink. The most common method for this transformation is the treatment of the 1,5-diketone with hydroxylamine hydrochloride in ethanol heated at reflux.⁶⁹ A side reaction that the 1,5-diketone can undergo under the mildly acidic conditions of this reaction is an aldol reaction, followed by elimination, to give an enone instead. Pre-forming a 1,5-bisoxime under basic conditions and then treating this intermediate with acid to generate the pyridine compound can prevent this unwanted side reaction.⁷⁰

Treatment of the 1,5-diketone **104** with hydroxylamine hydrochloride in ethanol heated at reflux led to the pyridine compound **120** very cleanly (Scheme 6.5). Unfortunately, the reaction conditions were acidic enough to remove both the MOM groups from the product, with the result that the product was very polar and difficult to handle. Attempts to buffer the reaction with various bases failed to prevent the loss of the MOM groups, while attempts to re-protect the material resulted in only one of the MOM groups being reinstalled.

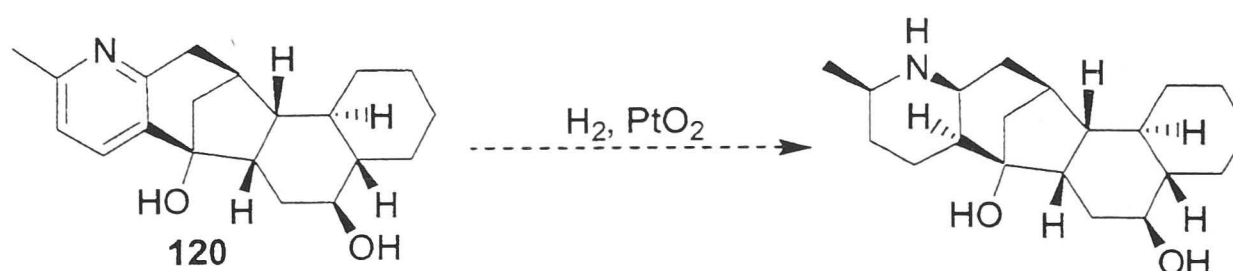
Scheme 6.5



The reduction of pyridine compounds by transition metal catalysed hydrogenation is an important industrial reaction, but is less common in small-scale synthesis due to the high pressures and temperatures that are often required. Nevertheless there are examples of this transformation in the literature,⁷¹ although there are very few examples of trisubstituted pyridines being reduced. This transformation was still considered as a possibility in this synthesis since the transition metal should deliver the hydrogen to just one face of the pyridine ring to give the all-*cis* substituted piperidine ring found in the natural product. In addition, the reactivity of the pyridine ring towards catalytic hydrogenation can be increased by formation of a pyridinium salt.⁷¹

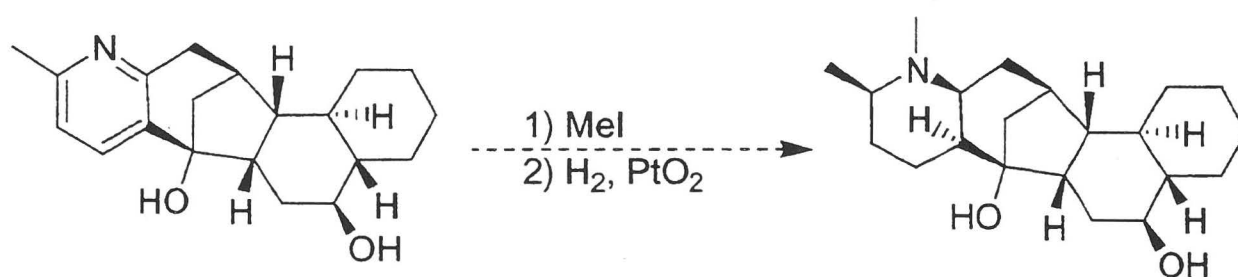
Attempts to reduce the pyridine compound 120 with $\text{Rh}/\text{Al}_2\text{O}_3$ or PtO_2 in ethanol or ethanol/acetic acid at 4 atmospheres of hydrogen were unsuccessful, with only starting material being returned (Scheme 6.6).

Scheme 6.6



The pyridine **120** was treated with methyl iodide in acetone at reflux to give material that may have been the methyl quaternary salt, although this very polar compound could not be purified, so definitive characterisation was not possible. Treatment of this material with PtO_2 or $\text{Rh}(\text{OH})_3$ in methanol at 4 atmospheres H_2 did not result any change in the ^1H -NMR spectra of the material (Scheme 6.7).

Scheme 6.7

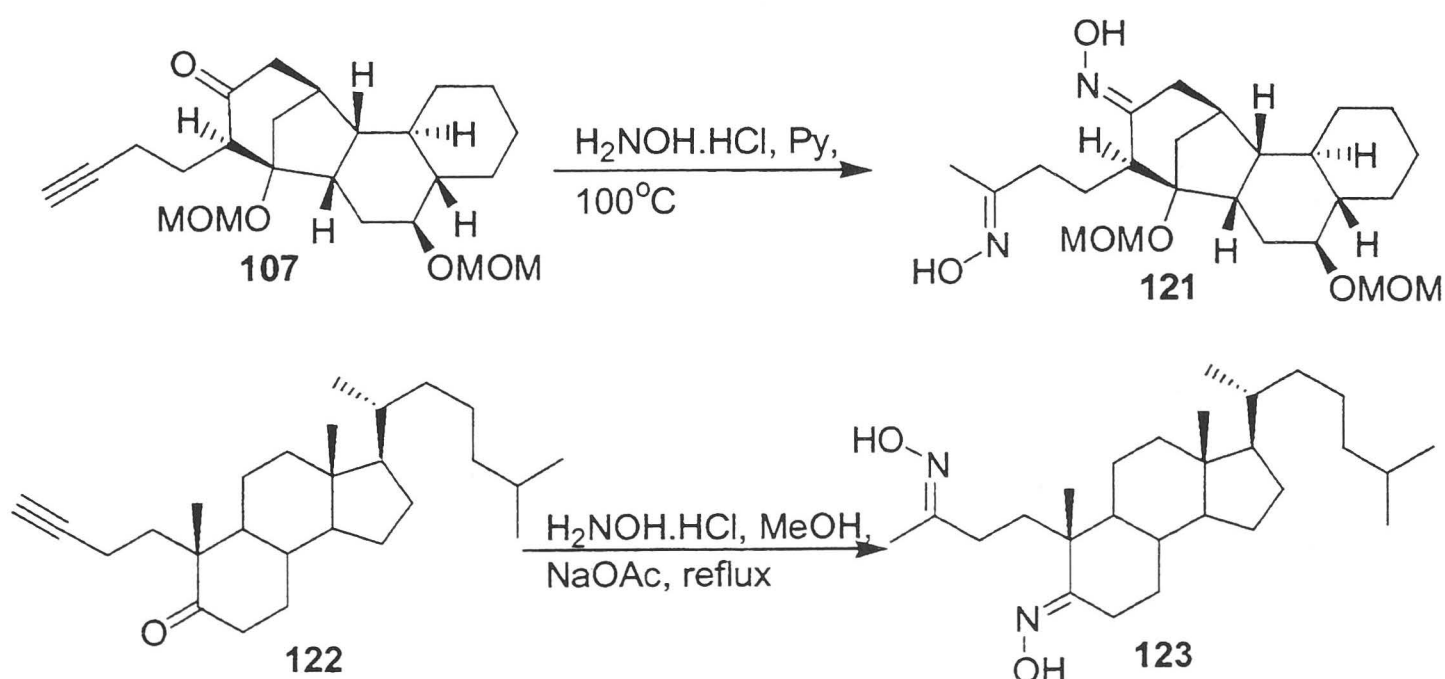


6.3 Bisoxime cyclisation

With the failure of the more common method of reductive amination to introduce nitrogen into the molecule, other sources of nitrogen such as hydroxylamine, sulfinylamines and azide were considered. Hydroxylamine is a common surrogate for amines in reductive aminations, as the intermediate oxime is quite stable, relative to the equivalent imine.

Treatment of the alkynyl ketone **107** with hydroxylamine hydrochloride in pyridine gave the 1,5-bisoxime **121**. The attack of the hydroxylamine on the alkyne was unexpected, but had been reported previously for the steroidal derivative **122** (Scheme 6.8).⁷²

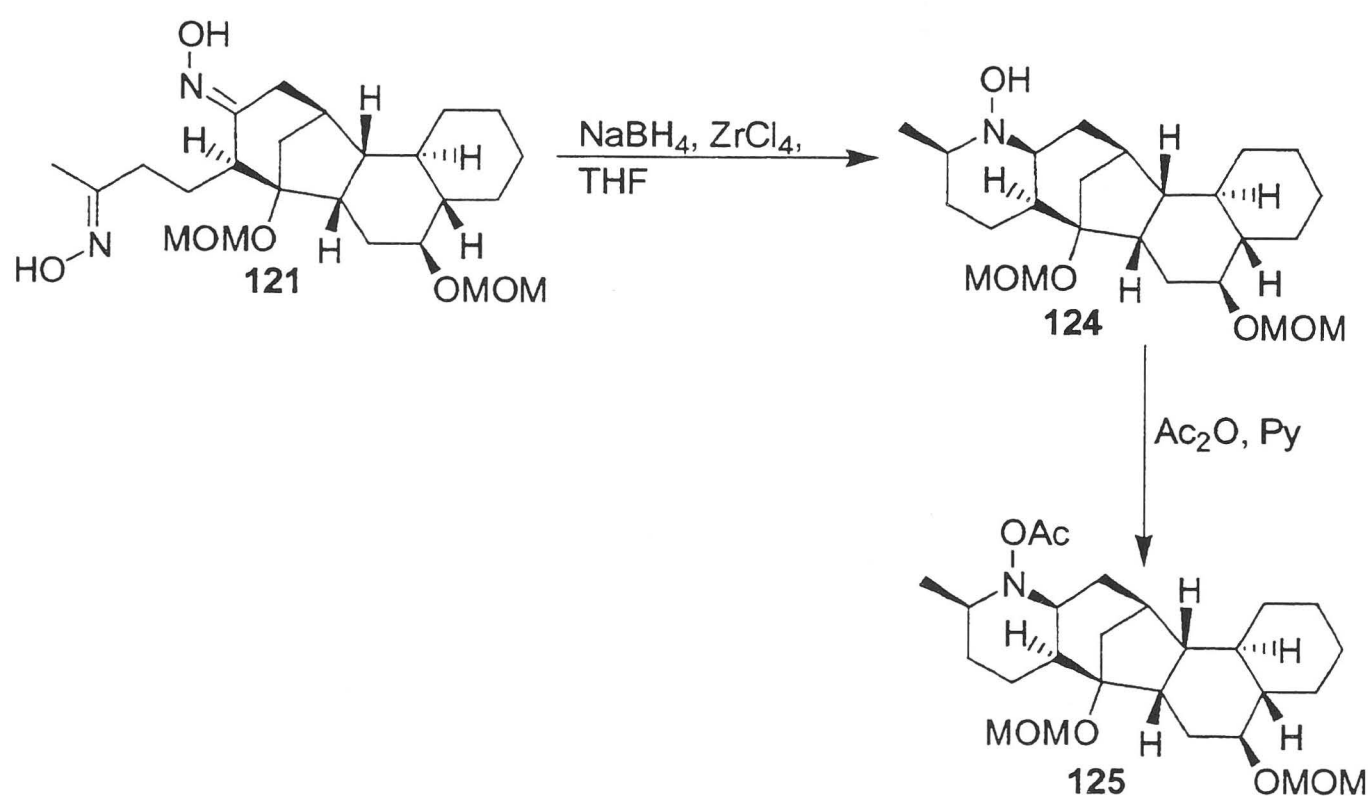
Scheme 6.8



Evidence was found in the ^{13}C -NMR spectrum that the bisoxime **121** was the product. There were no peaks in the spectra that correlated to the peaks expected for the alkyne at 70-90 ppm, while there were two peaks at 159.1 and 159.3 ppm, which correlate well with the shifts expected for the oxime carbons. In addition, a peak at 13.9 ppm could be attributed to the methyl group adjacent to the side chain oxime.

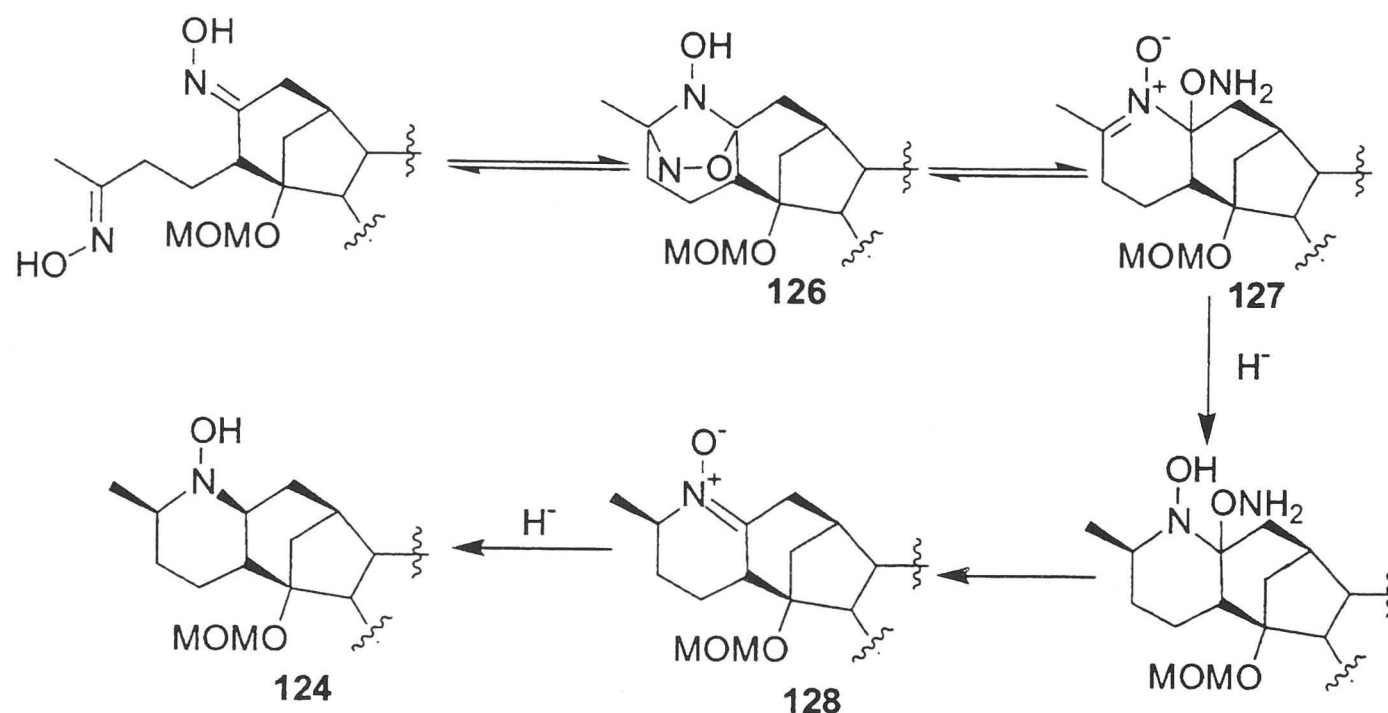
Attempts to reduce the bisoxime **121** with LiAlH_4 returned only starting material, but the use of a mixture of ZrCl_4 and NaBH_4 gave the hydroxy piperidine compound **124** (Scheme 6.9). This product was acetylated to give compound **125** by treatment with acetic anhydride and pyridine, for characterisation purposes.

Scheme 6.9



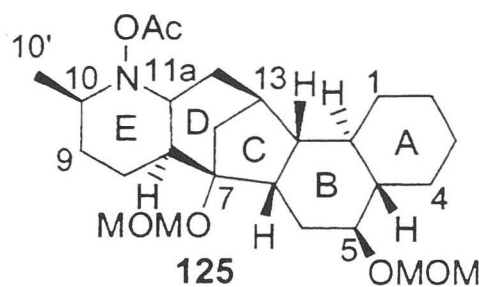
The mechanism for this reaction is postulated to proceed through the transient "oxadiazas" structure **126** (Scheme 6.10), which collapses to the nitron **127**.⁷² This nitron can then be reduced by the hydride source and converted to a second nitron **128**, which upon reduction would give the observed hydroxypiperidine compound **124**. It is interesting to note that the zirconium reagent was not required in the reaction of the steroidal bisoxime **123**, but was required for the reduction of the bisoxime **121**.

Scheme 6.10



The reaction gave only one major isomer, although there were many baseline peaks in the crude 1H -NMR spectra, indicating that other isomers were probably formed in trace amounts. The stereochemistry of the product was assigned by the use of 1D and 2D NMR techniques, the data from which are given below in Tables 6.2, 6.3 and 6.4.

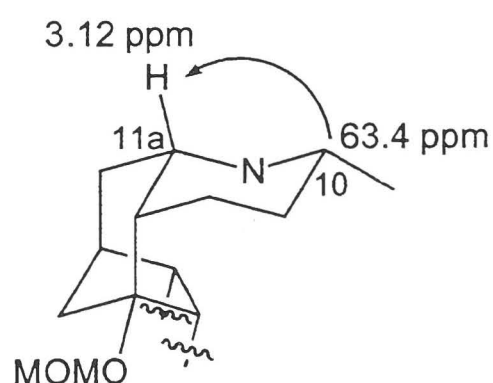
Table 6.2: ^{13}C and Hetero-correlation data for
N-acetoxypiperidine compound 125



C	ppm	H's (ppm) gHMQC	H's (ppm) gHMBC
CH ₃ CO ₂	19.4	2.05	
CH ₃ C'10	20.5	1.08	1.8

CH ₂ C8	22.3	2.22, 1.3	2.33, 2.04, 1.8, 1.55, 1.48, 1.14, 1.06, 0.86
CH ₂ C6, C2, C3	26.4	1.8, 1.65, 1.3, 1.15	2.7, 1.78, 1.38, 1.14, 1.0
CH ₂ See 26.4	26.45	See 26.4	See 26.4
CH ₂ See 26.4	26.7	See 26.4	See 26.4
CH ₂ C9	31.4	1.8, 1.55	2.33, 2.22, 1.3, 1.06
CH ₂ C1	32.5	1.8, 0.9	1.64, 1.3
CH ₂ C4	34.0	1.96, 1.00	3.5, 1.16, 0.82
CH ₂ C12	34.5	1.65, 1.48	3.1, 2.6, 2.14, 2.04, 1.32
CH C13	36.7	1.93	3.1, 2.7, 2.04, 1.66, 1.48, 1.32, 0.72
CH C6a	38.1	2.70	3.50, 2.33, 2.04, 1.91, 1.8, 1.32, 1.26
CH ₂ C14	39.2	2.05, 1.35	2.64, 2.33, 2.18, 1.91, 1.66, 1.48, 1.3, 1.16
CH C13b	39.3	0.72	See 39.2
CH C13a	44.1	2.66	2.7, 1.9, 1.8, 1.48, 1.32, 1.16, 0.72
CH C4a	44.8	1.18	3.5, 1.96
CH C7a	45.9	2.33	3.1, 2.70, 2.22, 2.05, 1.66, 1.55, 1.3
CH ₃ C5 MOM	55.1	3.40	4.7, 4.5
CH ₃ C7 MOM	55.9	3.39	4.65
CH C10	63.4	2.55	3.12, 2.22, 1.8, 1.3, 1.06
CH C11a	65.5	3.12	2.33, 2.22, 1.93, 1.65, 1.48
CH C5	78.1	3.50	4.7, 4.55, 1.8, 1.16
C C7	85.9		4.65, 3.1, 2.7, 2.3, 2.22, 2.05, 1.3
CH ₂ C7 MOM	92.2	4.66	3.39
CH ₂ C5 MOM	94.3	4.59, 4.74	3.5, 3.40
C CO ₂	171.9		

Assignment of the resonances arising from the D and E rings of the compound was straightforward, as the signals for C10 and C11a were quite obvious, at 63.4 and 65.5 ppm respectively. The hydrogens attached to these carbons, H10 and H11a, were also obvious, at 2.55 and 3.12 ppm respectively. In addition, the hydrogens on the methyl group C'10 gave rise to a distinctive doublet at 1.06 ppm in the ^1H -NMR spectra. The gHMBC spectra confirmed that the reductive cyclisation had indeed occurred, as there was a clear long range coupling from C10, at 63.4 ppm to H11a at 3.12 ppm. If the piperidine ring had not formed then it would not be possible to observe this long-range coupling.



The gHMBC data allowed the assignment of the rest of rings D and E in the following manner. Both C10 and C11a showed long-range coupling to 2.22 ppm. This signal at 2.22 ppm is associated with a carbon at 22.3 ppm which shows a long range coupling to H10' at 1.06 ppm, so this signal at 22.3 ppm must be attributed to C8. The only other carbon signal to show a long range coupling to 1.06 ppm is at 31.4 ppm, so that resonance must be the signal due to C9. The signal at 45.9 ppm shows long range coupling to 3.12 (H11a), 2.22 (H8) and 1.55 (H9) ppm, and so must be assigned to C7a.

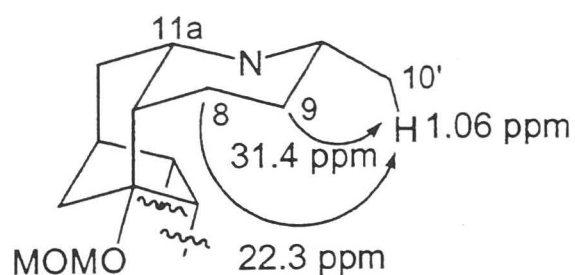
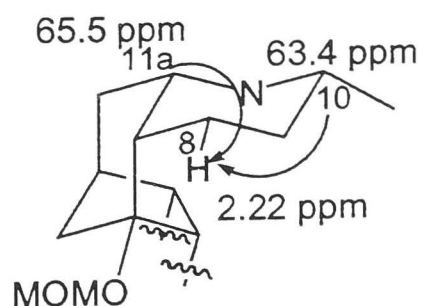


Table 6.3: ^1H and COSY data for *N*-acetoxypiperidine
compound 125

H	ppm	H's (ppm) COSY
H13b	0.72	2.6, 1.18, 0.9
H4, H1	0.84-1.04	0.98-1.3, 0.97, 0.72
H10'	1.06	2.52
H4a (H2, H3)	1.04-1.22	3.5, 2.62, 2.52, 1.88, 1.64, 1.34-0.92, 0.86, 0.72
H14, H8, H6	1.24-1.36	3.5, 2.7, 2.3, 2.22, 2.11, 2.04, 1.93, 1.8, 1.76, 1.64, 1.54, 1.34-0.92, 0.86
H12	1.48	3.1, 1.92, 1.62
H9	1.55	2.55, 2.22, 1.8, 1.3
H12 (H2, H3)	1.63-1.72	2.0, 1.90, 1.45, 1.3, 1.1, 0.95
H9, H1, H6 (H2, H3)	1.74-1.87	3.5, 2.7, 2.55, 2.2, 1.8, 1.55, 1.3, 1.1, 0.9, 0.72
H13	1.93	2.06, 1.66, 1.45, 1.3, 1.2, 0.98
H4	1.96	See 1.93
CH ₃ CO	2.04	
H14	2.04-2.09	1.93, 1.65, 1.3
H8	2.22	1.8, 1.55, 1.3
H7a	2.34	3.1, 1.3
H10	2.55	1.8, 1.55, 1.06
H13a	2.68	1.2, 0.72
H6a	2.70	1.8, 1.3
H11a	3.12	2.3, 1.45, 1.22
Me MOM	3.39	
Me MOM	3.40	
H5	3.50	1.8, 1.3, 1.18
MOM	4.59	4.74
MOM	4.66	
MOM	4.74	4.59

C11a shows a long range coupling to 1.65 and 1.48 ppm, which must be either C12 or C14. The COSY data allowed an unambiguous assignment of the signals to H12, due to the strong coupling between H11a at 3.12 ppm to 1.48 ppm. C11a also showed a long range coupling to 1.93 ppm, which was associated with a carbon signal at 36.7, this could be either C13 or C13a. The overlap of this hydrogen signal complicated assignment, but there was a clear signal in the COSY data between 1.93 ppm and the H12 signal at 1.48 ppm, indicating that this signal was due to C13. Long range couplings were observed between a signal at 2.05 ppm to C8 and C12, so this must be H14, with the other hydrogen coming at 1.3 ppm and the associated carbon at 39.2 ppm. COSY data supports this assignment, as well as backing up the assignment of H13, as there is signal between 2.05 ppm and 1.93 (H13), 1.65 (H12, W coupling) and 1.3 (H14) ppm.

The signal for H5 was distinct, at 3.50 ppm, and allowed assignment of the B ring. H5 showed three correlations in the COSY spectrum, to 1.8, 1.3 and 1.18 ppm. The signal at 1.18 ppm was associated with a CH at 44.8 ppm, and so must be C4a, while the 1.8 and 1.3 ppm signals must belong to C6. 1.3 and 1.8 ppm both show a strong coupling to 2.70 ppm, so this signal must belong to H6a with the associated C signal at 38.1 ppm. The signal at 2.70 ppm couples to an adjacent overlapping signal at 2.66, so this must be H13a. Both H13a and H4a couple to a signal at 0.72 ppm, so this was assigned to H13b. C1 and C4 were assigned by their coupling to H13b and H4a respectively. C2 and C3 could not be assigned due to overlapping signals.

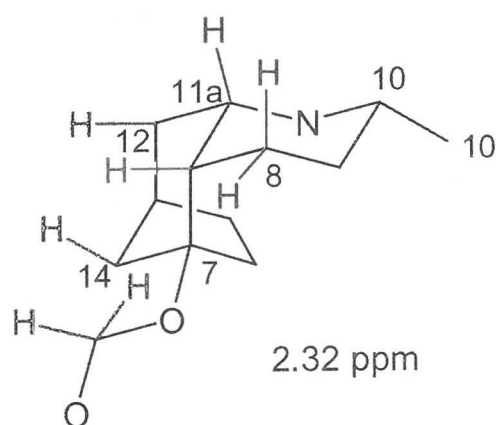
With the NMR resonances from the compound now almost fully assigned, the stereochemistry of the *N*-acetoxypiperidine ring could be deduced through the use of nOe experiments. Four signals were irradiated, at 3.12 (H11a), 2.55 (H10), 2.32 (H7a) and 1.06 (H10') ppm. The results are presented in Table 6.4.

Table 6.4: nOe data for *N*-acetoxypiperidine
compound 125

H	nOe's (s=strong, m=moderate, w=weak)
3.12 (H11a)	2.55(s), 2.32(s), 1.92(w), 1.66(s), 1.48(s), 1.32(m), 1.0(w)
2.55 (H10)	3.12(s), 1.80(w), 1.55(s), 1.3(s), 1.06(s)
2.32 (H7a)	4.67(m), 3.12(s), 2.22(w), 1.48(w), 1.3(s+w)
1.06 (H10')	2.55(s), 2.02(w), 1.96(w), 1.8(s+m), 1.66(s), 1.55(s)

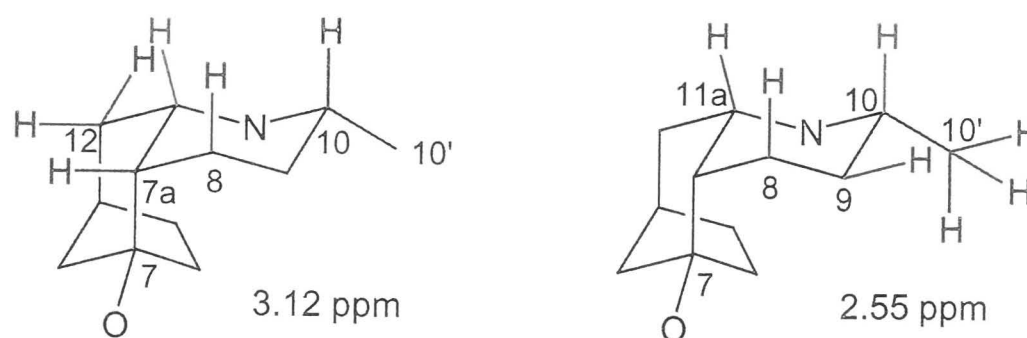
The first nOe spectrum to analyse was that for H7a at 2.32 ppm (Figure 6.1). This spectrum showed an nOe correlation from 2.32 ppm to 4.76 (CH₂-MOM), 3.12 (H11a), 2.22 (H8), 1.48 (H12) and 1.3 (H14) ppm. The correlation to H14 clearly shows that H7a is on the same face as the bridge.

Figure 6.1



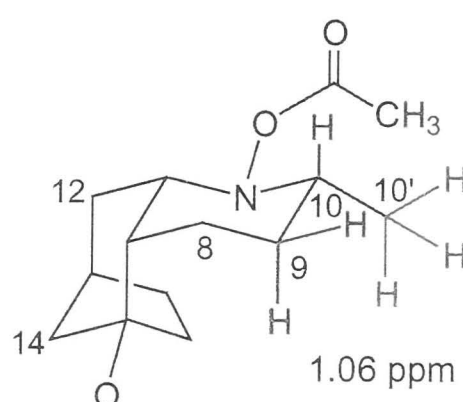
Analysis of the nOe spectra for H11a shows a correlation between 3.12 ppm and 2.55 (H10), 2.32 (H7a), 1.66 and 1.48 (H12), 1.32 (H8) ppm. This shows that H11a is on the same face of the piperidine ring as H10 and H7a, and therefore has the desired all *cis* conformation (Figure 6.2). This was backed up by the analysis of the nOe spectra for H10, which showed a correlation between 2.55 ppm and 3.12 (H11a), 1.55 (H9), 1.3 (H8) and 1.06 (H10') ppm.

Figure 6.2



Although the nOe spectra for H10' was complicated by overlapping peaks, it does show a correlation between 1.06 ppm and 2.55 (H10), 2.02 (CH_3CO_2), 1.8 and 1.55 (H9) ppm (Figure 6.3).

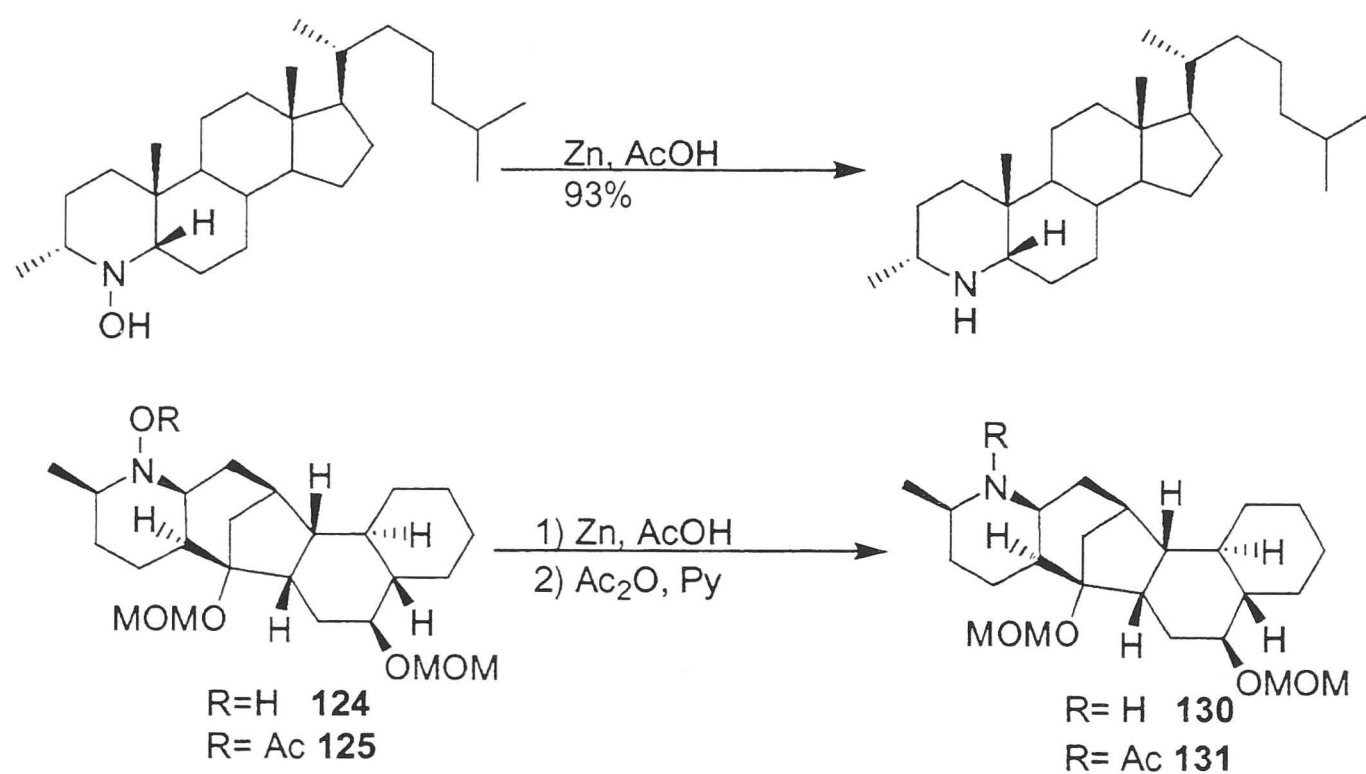
Figure 6.3



There was little evidence available for the presence of the *N*-acetoxy functional group, with the only source of information being I.R. spectrometry. The peak for the $\text{C}=\text{O}$ in the I.R. spectrum of this compound was at 1765 cm^{-1} , with a shoulder at 1732 cm^{-1} . This is near the region expected for an ester derivative, but well above that expected for an amide derivative, which normally absorbs between 1660 to 1690 cm^{-1} .

The reduction of the nitrogen-oxygen bond was carried out in a similar manner to that reported for the steroidal derivative **129**,⁷² by using zinc and acetic acid. Both the *N*-acetoxy compound **125** and *N*-hydroxy derivative **124** could be converted to the piperidine compound **130**, which was acetylated for purification and characterisation purposes to give the acetamide **131** (Scheme 6.11).

Scheme 6.11



The presence of the acetamide function was confirmed by the I.R. spectrum of the compound, which showed a strong absorption at 1638 cm^{-1} , attributed to the carbonyl absorption of the acetamide. There did not appear to be any scrambling of the stereochemistry at the positions adjacent to the nitrogen atom, as the $^1\text{H-NMR}$ spectra of the piperidine compound 130 was very similar to that of N-acetoxy compound 125, and in particular, the signals for H10 and H11a showed the same splitting pattern in both compounds 125 and 130.

Chapter 7

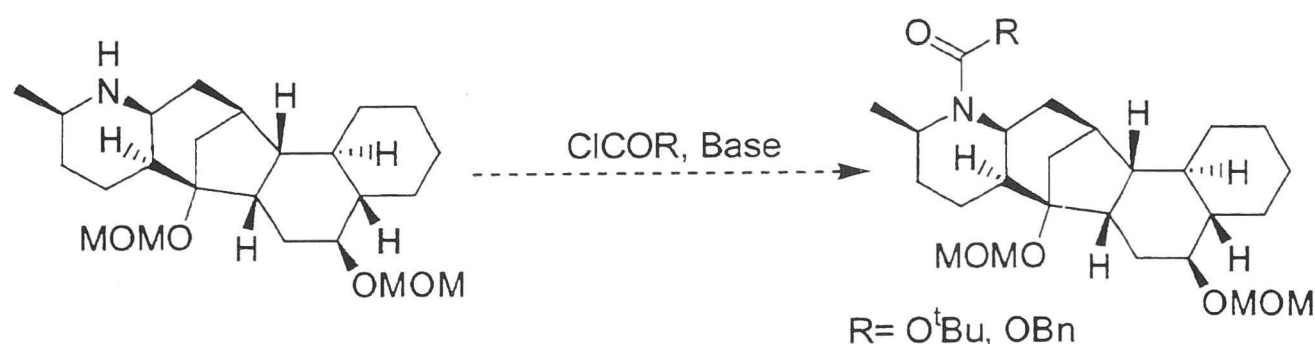
Future work and conclusions

7.1 Future work

In the previous chapter the syntheses of the piperidine compound **130** and the *N*-acetyl piperidine compound **131** were discussed. The remaining transformations required to elaborate compound **130** to alkaloid GB 13 (**4**) are protection of the nitrogen, deprotection of the hydroxyl groups, oxidation of the C5 hydroxyl, introduction of an alkene bond between C6 and C6a and deprotection of the nitrogen atom.

The most likely protecting group for the nitrogen will be an amide or a carbamate. Acetamide protecting groups were used extensively during the characterisation of this compound, and the use of acetamide as a protecting group in this synthesis will allow us to make comparisons directly with these previously synthesised derivatives. The acetamide protecting group is very robust however, and removal may be difficult. This is where a carbamate protecting group such as *t*-BOC or CBZ may find favour, as these groups can be removed under mildly acidic conditions or by hydrogenation, respectively.

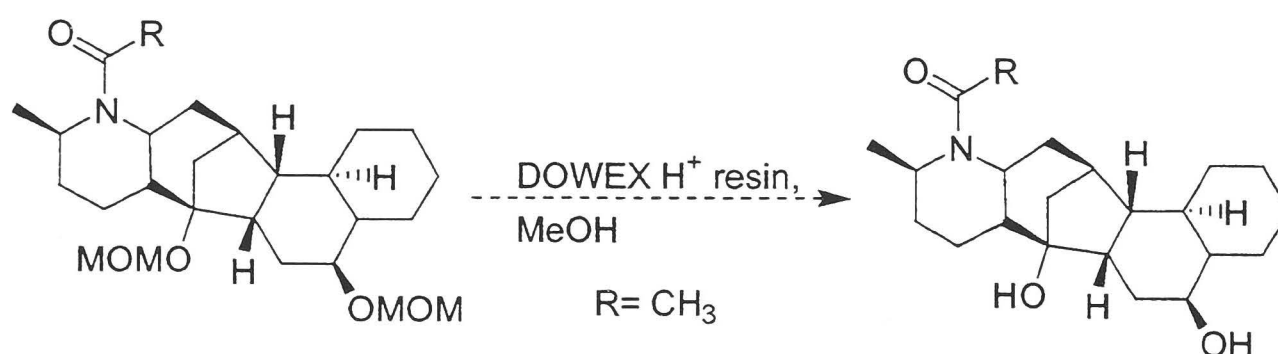
Scheme 7.1



The deprotection of the MOM groups is not expected to be troublesome, as these groups were in some cases difficult to keep intact, such as in the reaction to form the pyridine compound **120**. In addition to the standard MOM deprotection procedures that use aqueous acid, there are a number of other nucleophilic and Lewis acid catalysed procedures also available.

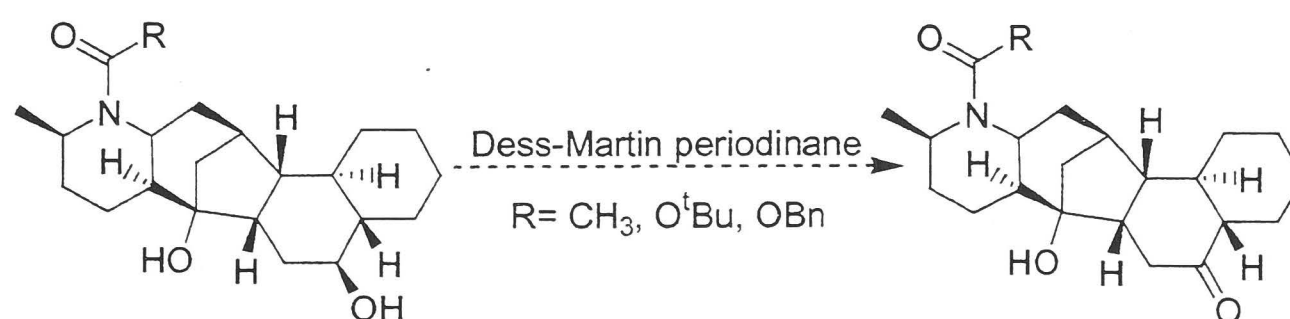
Preliminary results from the deprotection of the acetamide **131** using DOWEX H⁺ resin in methanol are encouraging (Scheme 7.2).

Scheme 7.2



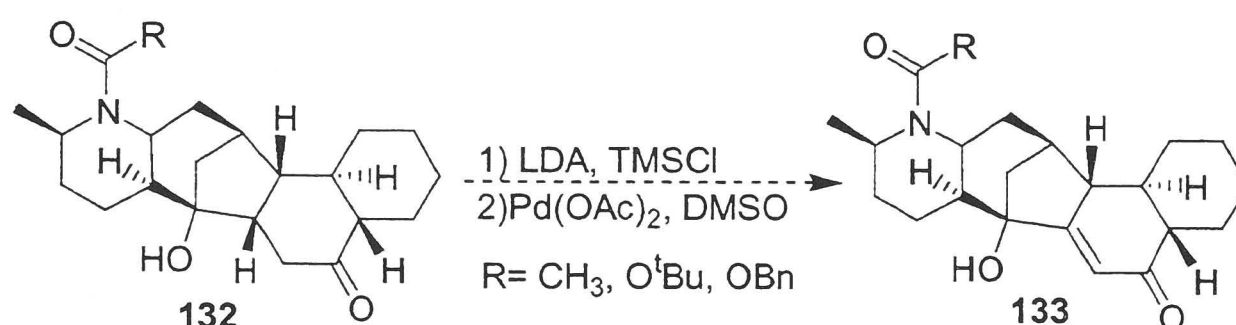
With the nitrogen protected and the hydroxyl groups deprotected the next step will be oxidation of the secondary C5 hydroxyl. This should be a straight forward transformation, with Dess-Martin periodinane being the reagent of choice (Scheme 7.3). It is not expected that the tertiary bridgehead hydroxyl will interfere with this reaction.

Scheme 7.3



The conversion of this newly formed C5 ketone to the enone has been explored previously on the analogous aromatic ketone **63**, as described in Chapter 3 Section 2. It is hoped that palladium (II) acetate mediated oxidative dehydrosilylation of the corresponding kinetic silyl enol ether of compound **132** will likewise result in the formation of the enone **133** (Scheme 7.4). Additional options for the formation of the enone involve trapping of the corresponding kinetic enolate with a suitable electrophile followed by elimination, as outlined in chapter 2.

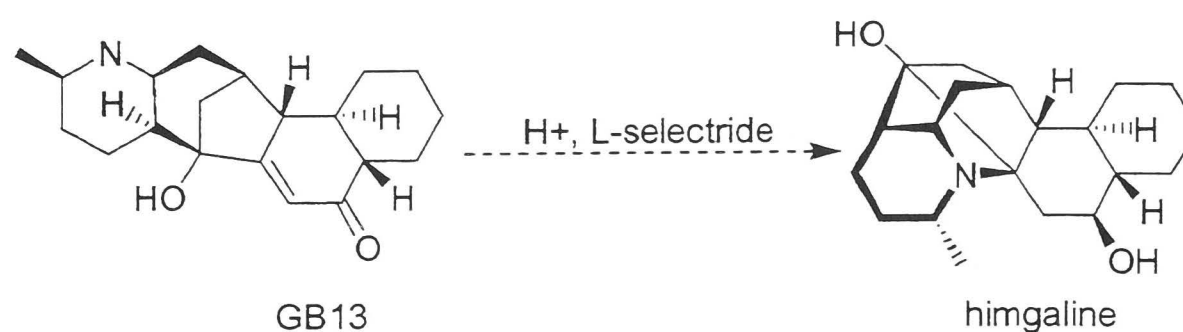
Scheme 7.4



Deprotection of the nitrogen atom will give alkaloid GB 13 (4), which we plan to compare with an authentic sample of the natural product. The conversion of alkaloid GB 13 to the *N*-methyl derivative himbadine has been carried out previously on material obtained from the natural source, by treatment with formic acid and formaldehyde.

As mentioned in chapter 1, alkaloid GB 13 had been converted to 5-epi himgaline by treatment with *p*-toluenesulfonic acid followed by lithium aluminum hydride. The reversal of this stereochemistry should not be difficult, and may be achieved by the use of a bulky hydride source (Scheme 7.5), or by an inversion using Mitsunobu or related procedures. This would complete the synthesis of alkaloids GB 13, himbadine and himgaline in racemic form.

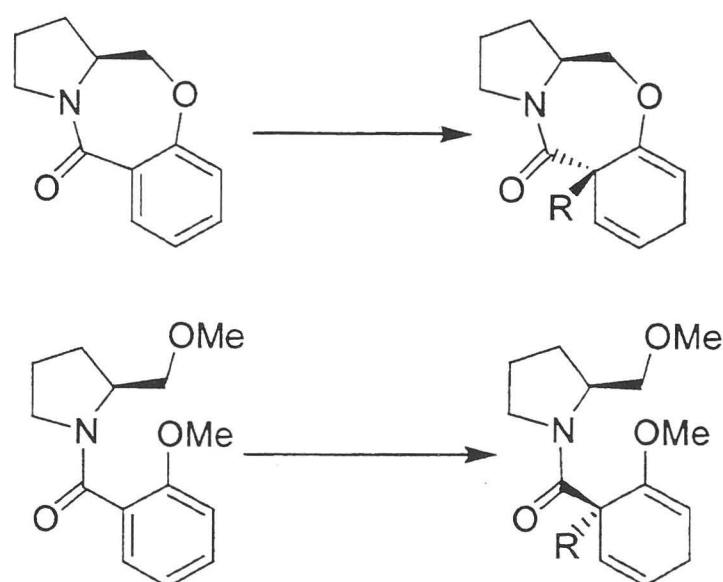
Scheme 7.5



An additional goal to pursue is the enantioselective synthesis of these alkaloids. This plan is based on the work of Schultz, who has shown that 2-

oxygenated benzamides can be diastereoselectively alkylated under Birch reductive conditions to give complementary enantiomers, after removal of the chiral auxiliary,⁷³ as outlined in Scheme 7.6.

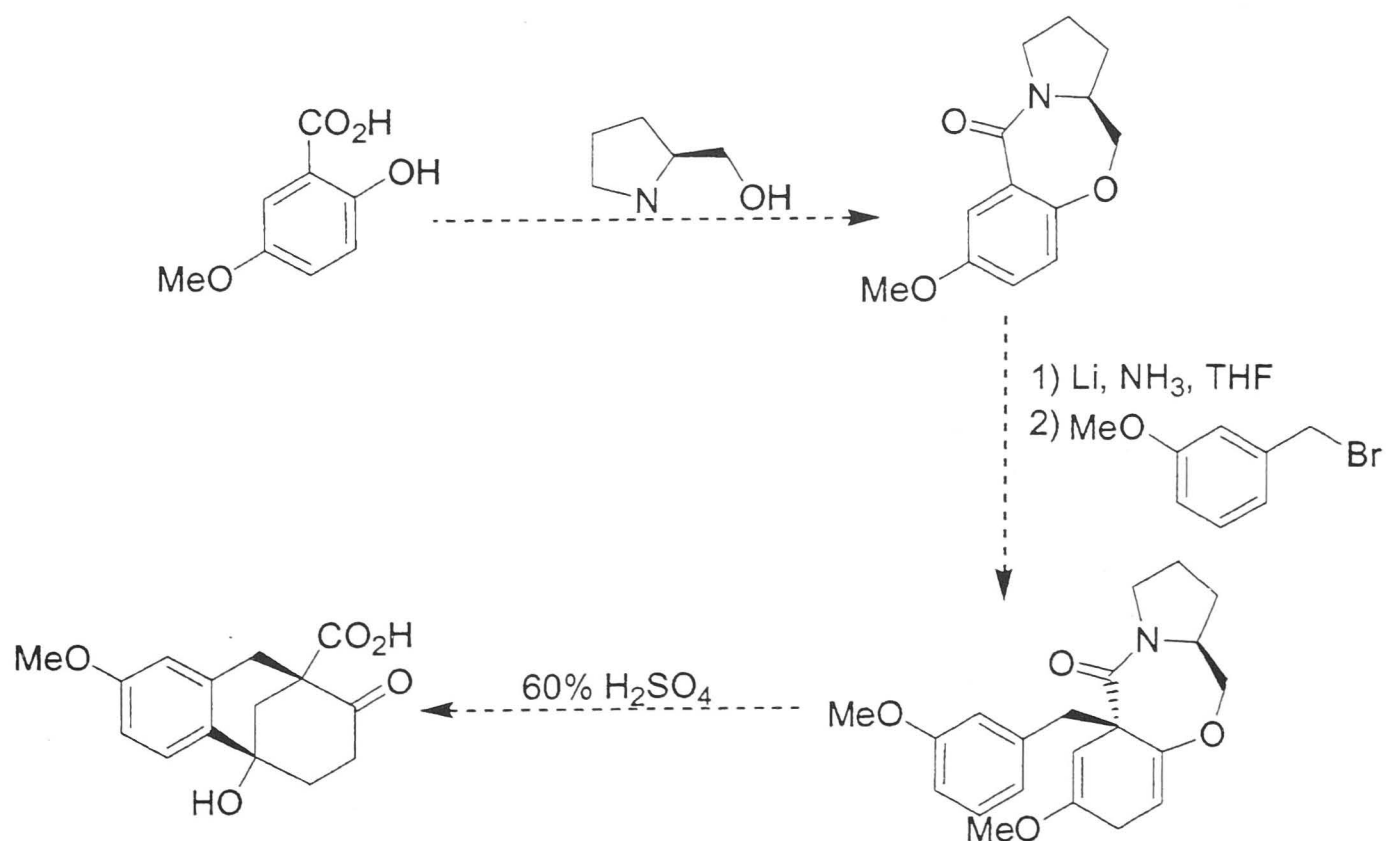
Scheme 7.6



R = alkyl, benzyl and allyl, ee > 95%

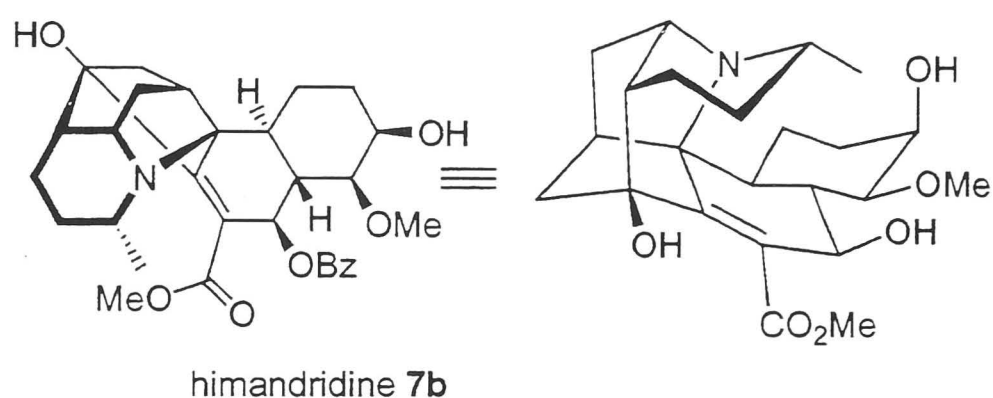
It is a reasonable expectation that the 2,5-dioxygenated benzamides will exhibit the same results as were achieved with the 2-oxygenated benzamides, allowing the enantioselective synthesis of the natural products, as outlined in Scheme 7.7.

Scheme 7.7



In a separate, but related project, lies the synthesis of the hexacyclic ester alkaloids **7a-o**, represented by himandridine **7b**. It has been recognised that some of the intermediates from the current synthesis could be used to synthesise these alkaloids.

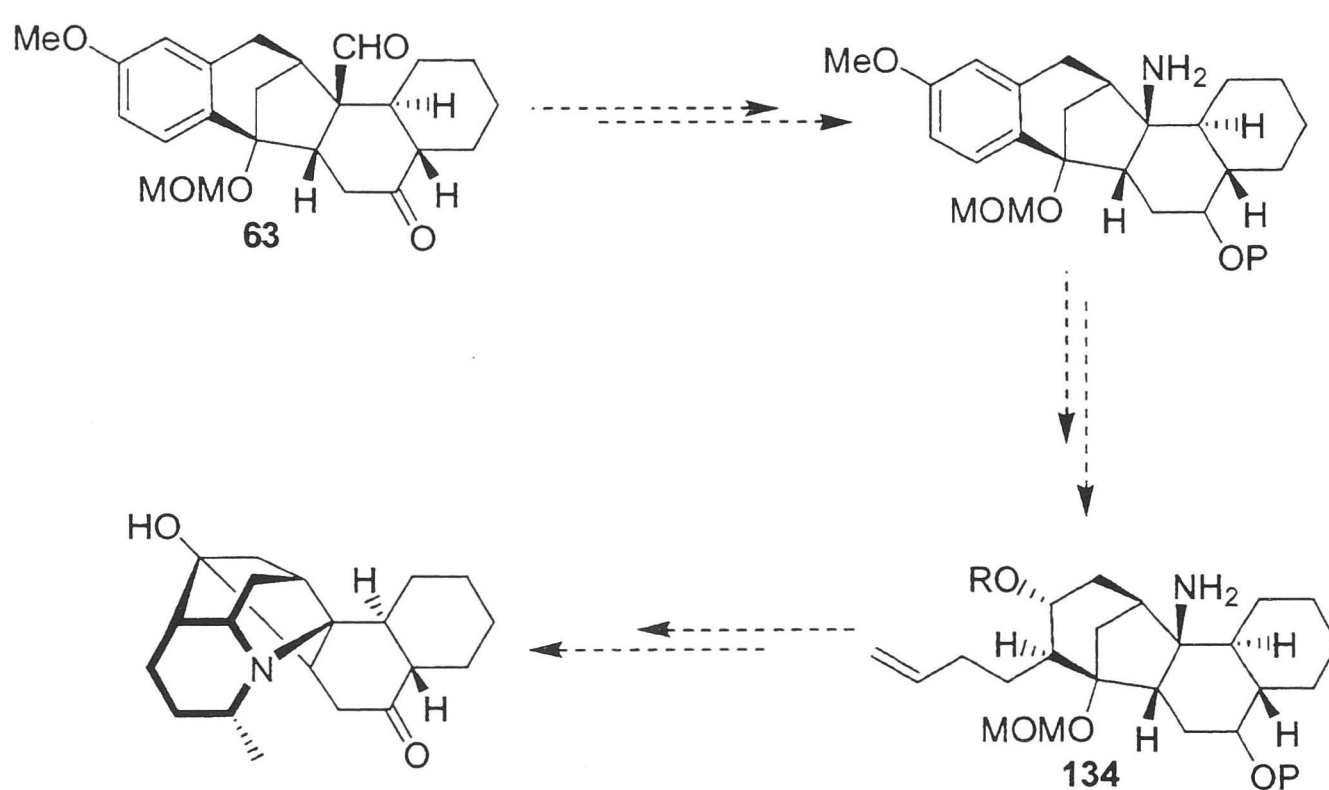
Figure 7.1



The aldehyde intermediate **63** could be used for a model study on the synthesis of the hexacyclic cage structure, as outlined in Scheme 7.8. The aldehyde function could be converted to an amine function by oxidation to an acid derivative, followed by a Curtis or Hoffmann rearrangement. Reduction of the aromatic ring, followed by ring cleavage and functional group manipulation could then lead to compound **134**, which may then cyclise to the hexacyclic cage structure found in the natural products.

The total synthesis of the hexacyclic ester alkaloids could ultimately be achieved by using a suitably functionalised analogue of the diene **60** in the Diels-Alder reaction to give a derivative of compound **134** with functionality in place to generate the oxygen functionalities on the decalin ring system found in the natural products.

Scheme 7.8



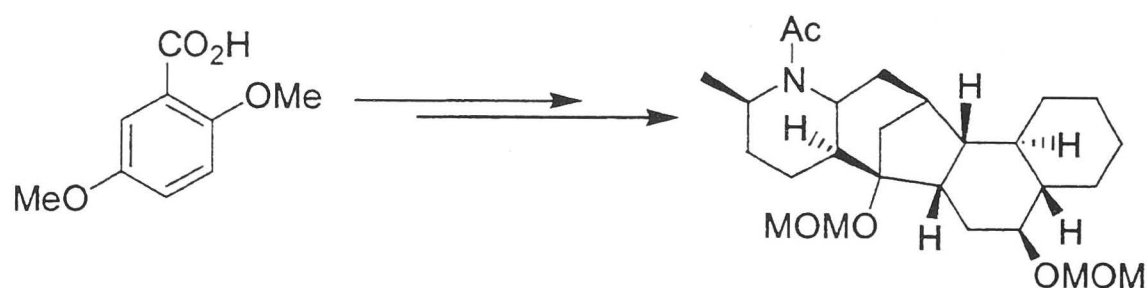
7.2 Summary and conclusions

The art of synthetic organic chemistry has evolved rapidly over the past forty years, and modern synthetic methods allow the rapid and efficient synthesis of a wide variety of synthetic targets using highly convergent approaches. Yet there are still targets that are a challenge for modern synthetic methods, such as caged and highly strained structures that do not lend themselves well to convergent synthesis. The work reported in this thesis attempted to address some of these issues by showing that a strained [3.2.1]bicyclooctane derivative may be synthesised and carried through a complex synthesis without detrimental effect, and may be further elaborated to give complex caged structures that are uncommon targets in modern synthetic literature.

This work also demonstrates the utility of methoxybenzenoids as synthons for the preparation of non-aromatic systems. The key [3.2.1]bicyclooctane system was synthesised by a Birch reductive alkylation of 2,5-dimethoxy benzoic acid, with the carbons from this aromatic compound being incorporated into the strained cyclopentane ring of the intermediates in this synthesis. Furthermore, a second aromatic residue, a 3,4-disubstituted methoxybenzenoid, was carried through a large portion of the synthesis and was subject to metal hydrides, ultraviolet radiation, strong acids, strong bases, nucleophilic and electrophilic conditions and even dissolving metal reduction, all without significant problems or decomposition. This methoxybenzenoid was then converted by Birch reduction and oxidative cleavage to several different acyclic and cyclic functionalities, including a 5-keto-alkyne, a 5-keto-ester, a pyridine and a 1,5-diketone. This aromatic residue was ultimately converted to the reactive, all *cis* piperidine ring found in the natural products. These results underline the versatility of this synthon as a stable precursor to reactive functionality.

In summary, this thesis has described the synthesis of an advanced intermediate toward the synthesis of the *Galbulimima belgraveana* alkaloids GB 13, himbadine and himgaline. The *N*-acetylpiperidine compound **131** has been synthesised in 22 steps and 1.8% overall yield from the readily available 2,5-dimethoxy benzoic acid. An additional four steps are likely to be required to synthesize alkaloid GB 13, and five steps to synthesize the alkaloids himbadine and himgaline.

Scheme 7.10



Chapter 2 described the synthesis of a versatile intermediate [3.2.1]bicyclooctane derivative **43** that should serve as a common intermediate in the total synthesis of all of the penta- and hexa-cyclic *Galbulimima belgraveana* alkaloids. This [3.2.1]bicyclooctane was further elaborated into a pentacyclic aldehyde intermediate **63** by the use of a highly diastereoselective Diels-Alder reaction.

Chapter 3 discussed several methods for the removal of a carbon atom from a quaternary centre, with the successful route being reductive decyanation by lithium metal in liquid ammonia. Also discussed in this chapter was the concurrent Birch reduction of the aromatic ring of compound **71** during the reductive decyanation, when ethanol was added to the reaction mixture.

In Chapter 4, several improvements to the synthesis were discussed, resulting in a significant increase in the overall yield and a shortening of the synthesis.

Methods for the cleavage of the cyclic enone **93** to various acyclic ketone derivatives were discussed in Chapter 5. Methods covered included ozonolysis, ruthenium tetroxide/sodium periodate cleavage and an Eschenmoser fragmentation. The Eschenmoser fragmentation was low yielding when literature methods were used, but the introduction of the novel 4-nitrobenzenesulfonylhydrazide resulted in a vastly improved yield for this reaction.

In the first part of Chapter 6, a number of failed attempts to synthesis the piperidine ring found in the natural products were discussed. The final section of chapter 6 described an unusual reductive cyclisation of a bis-oxime to give an *N*-hydroxypiperidine compound **123** with the same relative stereochemistry found in the natural product. This was further elaborated to the piperidine compound **130**. In section 7.1, the final steps required to convert the piperidine compound to the desired natural products are outlined.

Chapter 8

Experimental Section

8.1 General Experimental Details

Melting points were recorded on a reichert hot-stage and are uncorrected. Microanalyses were carried out by the Australian National University Analytical Services Unit, Canberra.

Low resolution EI mass spectra (70 eV) and high resolution accurate mass measurements were recorded on a VG Micromass 7070F double focussing mass spectrometer. The molecular ion (M^+), if present, and intense lower mass ions are reported. The data is presented in the following format: m/z value (relative intensity as a percentage of base peak).

Infrared spectra were recorded on a Perkin-Elmer 683 Infrared spectrophotometer as a thin film on NaCl disks, unless otherwise stated.

^1H -NMR spectra were recorded on the following instruments: Varian Gemini 300 and Varian Mercury 300 at 300 MHz and Varian Inova 500 at 500 MHz. ^{13}C -NMR spectra were recorded as attached proton test (APT) spectra (unless otherwise stated) on the following instruments: Varian Gemini 300 at 75.5 MHz and Varian Inova 500 at 125 MHz. Chemical shifts are reported as δ values in parts per million. The internal reference for all ^1H spectra recorded in CDCl_3 was the residual peak of CHCl_3 (7.26 ppm). For ^1H spectra recorded in d_6 -acetone the residual peak of d_5 -acetone (2.05 ppm) was used as the internal reference. The internal reference for all ^{13}C spectra recorded in CDCl_3 was the central peak of CDCl_3 (77.0 ppm). For ^{13}C spectra recorded in CD_3OD the spectra was referenced to the central peak of CD_3OD (49.0 ppm).

Two dimensional NMR experiments were carried out using the following instruments: Varian Mercury 300 and Varian Inova 500. The pulse sequences used were homonuclear ($^1\text{H}/^1\text{H}$) correlation spectroscopy (COSY), gradient

double quantum filtered homonuclear ($^1\text{H}/^1\text{H}$) correlation spectroscopy (gDQCOSY), heteronuclear ($^{13}\text{C}/^1\text{H}$) multiple bond correlation spectroscopy (HMBC), heteronuclear ($^{13}\text{C}/^1\text{H}$) multiple quantum correlation spectroscopy (HMQC) and phase sensitive Nuclear Overhauser and exchange spectroscopy (PS- $^1\text{H}/^1\text{H}$ -NOESY).

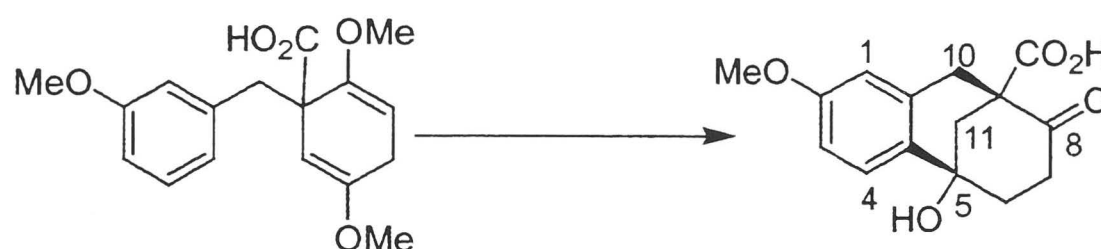
Analytical thin layer chromatography (tlc) were conducted on aluminum backed plates coated with Merck Kieselgel KG60F-254. The developed plates were visualised under short wave ultraviolet light and stained with phosphomolybdic acid and cerium sulphate in methanol/ H_2SO_4 at 180°C . Flash chromatography was conducted according to the methods of Still and co-workers⁷⁴ using Merck Kieselgel 60 as the absorbant and analytical reagent grade (AR) solvent as indicated.

All reagents were used as supplied by Aldrich Chemical Company unless otherwise stated. THF, Et_2O and benzene were purified by distillation from sodium metal and benzophenone. DCM, $i\text{Pr}_2\text{NEt}$ and NEt_3 were purified by distillation from CaH_2 . Methanol was purified by distillation from magnesium methoxide. DMF and DMSO were dried over 4\AA molecular sieves before use. KO^tBu was purified by sublimation prior to use.

All reactions were performed under a dry nitrogen atmosphere and reaction temperature refers to the external bath temperature, unless otherwise stated. All organic extracts were dried with anhydrous magnesium sulfate unless otherwise stated. After filtration of solutions from the drying agent the bulk of the solvent was removed on a Buchi rotary evaporator with a water aspirator. Samples were then subjected to high vacuum to remove any remaining solvent.

8.2 Experimental details

(5*RS*,9*SR*)-5,6,7,8,9,10-Hexahydro-5-hydroxy-2-methoxy-8-oxo-5,9-methanobenzocyclooctene-9-carboxylic acid (39a)



A solution of **38a** (36 g) in acetone (400 ml) was added dropwise to a stirred aqueous solution of sulfuric acid (60% by vol., 1200 ml) at 0°C, so as to maintain the reaction temperature below 5°C. The reaction was stirred for a further 2 h at 0°C and was then poured slowly onto ice (2.5 l) and the pH raised to 1 with ice cold dilute sodium hydroxide (1 M). The aqueous solution was extracted 4 times with ethyl acetate (4x500 ml) then the combined organic extracts were washed with brine, dried, and the solvent removed *in vacuo*. The residue was recrystallised from acetone/petroleum spirit to afford white crystals of the title compound (26 g, 80%).

R_f: 0.45 EtOAc, AcOH 1%

m.p. 184 °C (decomp.)

IR: (neat) 3410, 2946, 1706, 1610, 1501 cm⁻¹

¹H NMR: (acetone d₆): 2.06-2.11 (m, 2H, H6, H11) 2.31-2.49 (m, 3H, H7, H6) 2.81 (dd, 1H, *J*=12.5, 1.8 Hz, H11) 3.14 (d, 1H, *J*=18.1 Hz, H10) 3.47 (d, 1H, *J*=18.1 Hz, H10) 3.91 (s, 3H, OMe) 6.87 (d, 1H, *J*=2.7 Hz, H1) 6.98 (dd, 1H, *J*=8.7, 2.6 Hz, H3) 7.74 (d, 1H, *J*=8.7 Hz, H4)

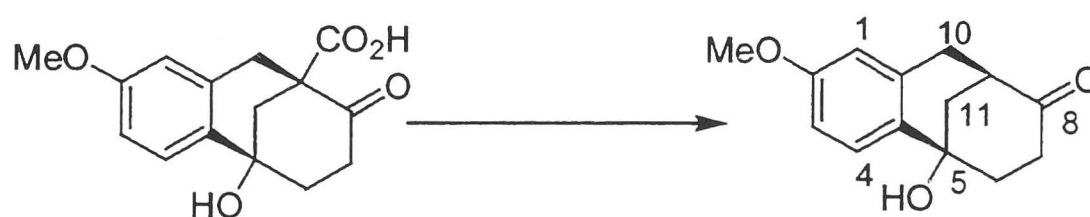
^{13}C NMR: (acetone d_6): 34.0 (CH_2), 35.4 (CH_2), 39.7 (CH_2), 40.4 (CH_2), 52.9 (CH_3), 56.4 (C), 68.1 (C), 110.4 (CH), 111.5 (CH), 124.4 (CH), 132.2 (C), 133.1 (C), 157.3 (C), 170.5 (C), 204.0 (C)

MS (EI) m/z : 276 (M^+ , 5%), 232 (9), 219 (44), 175 (100), 160 (17), 115 (13)

HRMS m/z calc'd for $\text{C}_{15}\text{H}_{16}\text{O}_5$: 276.0998, found 276.0999

Analysis calc'd for $\text{C}_{15}\text{H}_{16}\text{O}_5$: C 65.21, H 5.84 found: C 65.04, H 5.50

(5*RS*,9*RS*)-5,6,7,8,9,10-Hexahydro-5-hydroxy-2-methoxy-8-oxo-5,9-methanobenzocyclooctene (51)



Carboxylic acid **39a** (16g) was suspended in acetic acid (400 ml) and water (50 ml) and the solution heated under reflux for 16 hour. The acetic acid was removed *in vacuo* and the residue was dissolved in ethyl acetate (800 ml). This solution was washed with dilute sodium hydroxide (1M, 500 ml), water (500 ml) and brine (500 ml), then dried and evaporated *in vacuo* to give the decarboxylated material as a clear oil that solidified on standing (12 g, 89%).

R_f: 0.52 EtOAc 80%, Pet. Sp. 20%

IR: (neat) 3416, 2935, 1710, 1608, 1499 cm^{-1}

^1H NMR: (CDCl_3): 1.92-2.03 (m, 2H) 2.09-2.22 (m, 3H) 2.23-2.39 (m, 2H) 2.77 (d, 1H, $J=17.9$ Hz, H10) 2.93 (m, 1H, H9) 3.20 (dd, 1H, $J=17.9$ Hz, $J=6.7$ Hz,

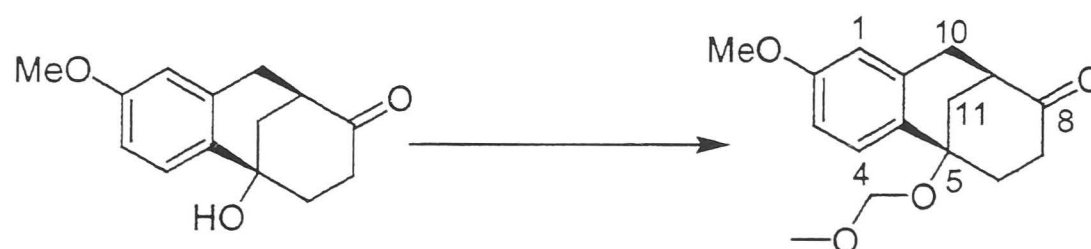
H10) 3.79 (s, 3H, OMe) 6.61 (d, 1H, $J=2.6$ Hz, H1) 6.84 (dd, 1H, $J=8.6$ Hz, $J=2.6$ Hz, H3) 7.60 (d, 1H, $J=8.7$ Hz, H4)

^{13}C NMR: (CDCl_3): 32.2 (CH_2), 36.4 (CH_2), 38.8 (CH_2), 40.4 (CH_2), 45.2 (CH), 54.4 (CH_3), 68.8 (C), 111.6 (CH), 112.3 (CH), 125.4 (CH), 133.6 (C), 134.4 (C), 158.0 (C), 213.1 (C)

MS (EI) m/z : 232 (M^+ , 34%), 189 (33), 175 (100), 160 (21), 147 (8), 115 (10), 84 (6)

HRMS m/z calc'd for $\text{C}_{14}\text{H}_{16}\text{O}_3$: 232.1099, found 232.1098

(5*RS*,9*RS*)-5,6,7,8,9,10-Hexahydro-2-methoxy-5-methoxymethoxy-8-oxo-5,9-methanobenzocyclooctene (42)



Compound **51** (26 g), DIPEA (36 ml) and DMAP (4.6 g) were dissolved in dichloromethane (1.5 l) and the solution cooled to 0°C with an ice bath. MOM chloride (26 ml) was added dropwise to the cooled solution and after the addition was complete the ice bath was removed and the reaction stirred for 16 h at room temperature. The excess of MOM chloride was quenched by the addition of aqueous sodium hydroxide solution (0.5 M, 300 ml) followed by stirring for 1 h at room temperature. The mixture was diluted with dichloromethane (1 l), washed with water (1.5 l), aqueous HCl (1 M, 1.5 l), water (1.5 l) and brine (1 l). The organic layer was then dried and the solvent removed *in vacuo* to give the protected compound as a clear oil (30 g, 97%).

R_f: 0.50 EtOAc 50%, Pet. Sp. 50%

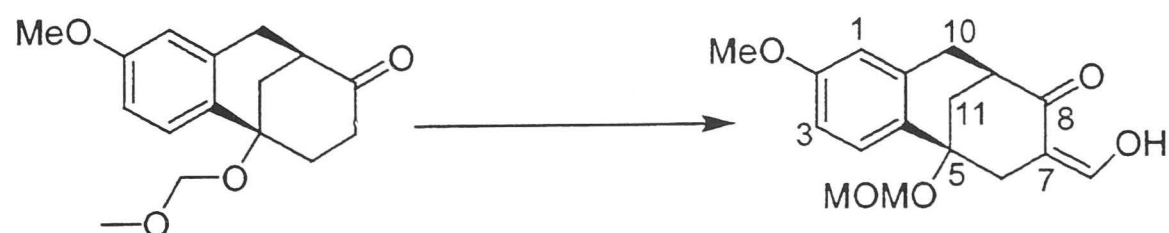
¹H NMR: (CDCl₃): 1.95-2.01 (m, 2H, H6, H11) 2.20-2.36 (m, 3H, H7, H6) 2.46 (dt, 1H, *J*=12.7 Hz, *J*=3.0 Hz, H11) 2.73 (d, 1H, *J*=18.0 Hz, H10) 2.94 (s, 1H, H9) 3.19 (dd, 1H, *J*=18.0 Hz, *J*=6.8 Hz, H10) 3.41 (s, 3H, OCH₂OCH₃) 3.79 (s, 3H, OMe) 4.62 (d, 1H, *J*=7.4 Hz, OCH₂OCH₃) 4.78 (d, 1H, *J*=7.4 Hz, OCH₂OCH₃) 6.61 (d, 1H, *J*=2.2 Hz, H1) 6.82 (dd, 1H, *J*=8.6 Hz, *J*=2.6 Hz, H3) 7.42 (d, 1H, *J*=8.6 Hz, H4)

¹³C NMR: (CDCl₃): 32.6 (CH₂), 35.6 (CH₂), 36.6 (CH₂), 40.1 (CH₂), 45.3 (CH), 54.6 (OCH₃), 54.9 (OCH₃), 75.7 (C), 91.5 (CH₂), 112.2 (CH), 112.9 (CH), 125.8 (CH), 130.8 (C), 136.6 (C), 158.5 (C), 212.1 (C)

MS (EI) *m/z*: 276 (M⁺, 11%), 219 (100), 189 (58), 175 (29), 159 (20), 115 (18)

HRMS *m/z* calc'd for C₁₆H₂₀O₄: 276.1362, found 276.1362

(5*SR*,9*RS*)-5,6,7,8,9,10-Hexahydro-7-hydroxymethylene-2-methoxy-5-methoxymethoxy-8-oxo-5,9-methanobenzocyclooctene (54)



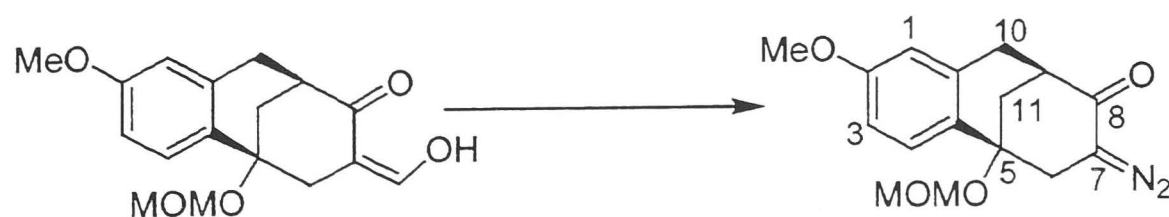
Sodium hydride (60% in paraffin oil, 15 g) was washed with petroleum spirit, suspended in THF (500 ml), and the solution cooled to 0°C. Ketone **42** (10 g) was dissolved in THF (100 ml) and this solution added slowly to the sodium hydride suspension. After stirring for 5 minutes ethyl formate (25 ml) was added and the solution stirred a further 1 h at 0°C. The cooling bath was removed and the solution stirred at room temperature for 16 h.

Methanol (20 ml) was added to quench the excess of sodium hydride and the solution was diluted with water (400 ml) and acidified to pH 1 with dilute HCl (2 M). The solution was extracted with ethyl acetate (3x 400 ml) and the organic layers combined and washed with brine, dried and the solvent removed *in vacuo* to give the crude product which was used in the next step without purification.

^1H NMR: (CDCl_3): 2.10 (ddd, 1H, $J=12.3$ Hz, $J=4.5$ Hz, $J=2.0$ Hz, H11) 2.37 (dt, 1H, $J=12.4$ Hz, $J=2.3$ Hz, H11) 2.52 (dd, 1H, $J=14.2$ Hz, $J=2.6$ Hz, H6) 2.90 (d, 1H, $J=14.3$ Hz, H6) 2.97 (m, 2H, H10, H9) 3.16 (dd, 1H, $J=17.1$ Hz, $J=5.9$ Hz, H10) 3.41 (s, 3H, OCH_2OCH_3) 3.77 (s, 3H, OMe) 4.56 (d, 1H, $J=7.3$ Hz, OCH_2OCH_3) 4.71 (d, 1H, $J=7.3$ Hz, OCH_2OCH_3) 6.55 (d, 1H, $J=2.6$ Hz, H1) 6.79 (dd, 1H, $J=8.7$ Hz, $J=2.6$ Hz, H3) 7.41 (d, 1H, $J=8.7$ Hz, H4) 8.58 (s, 1H, C(OH)H)

^{13}C NMR: (CDCl_3): 32.9 (CH_2), 34.4 (CH_2), 37.6 (CH), 39.7 (CH_2), 54.4 (CH_3), 54.8 (CH_3), 75.6 (C), 91.3 (CH_2), 105.9 (C), 112.2 (CH), 112.9 (CH), 126.2 (CH), 131.0 (C), 136.2 (C), 158.3 (C), 183.5 (C), 188.3 (CH)

(5*SR*,9*RS*)-5,6,7,8,9,10-Hexahydro-7-diazo-2-methoxy-5-methoxymethoxy-8-oxo-5,9-methanobenzocyclooctene (53)



The crude hydroxymethylene compound **54** (12 g) and triethylamine (10 ml) were dissolved in acetonitrile (700 ml) and the solution cooled to 0°C. 4-Nitrobenzenesulfonylazide (11 g) was added to the cooled solution in one portion and the cooling bath removed. After stirring at room temperature for 2 hours, aqueous sodium hydroxide (1M, 300 ml) was added and the

solvent removed *in vacuo* at room temperature. The aqueous solution obtained was extracted with ethyl acetate (3x 300 ml), the organic layers were combined and washed with aqueous sodium hydroxide (1M, 2x 400 ml), water (400 ml), brine (400 ml) and then dried and the solvent removed *in vacuo* to give the crude diazo ketone. This was usually used without purification in the next step, but could be purified, if desired, by column chromatography (ethyl acetate/petroleum spirit 3:1).

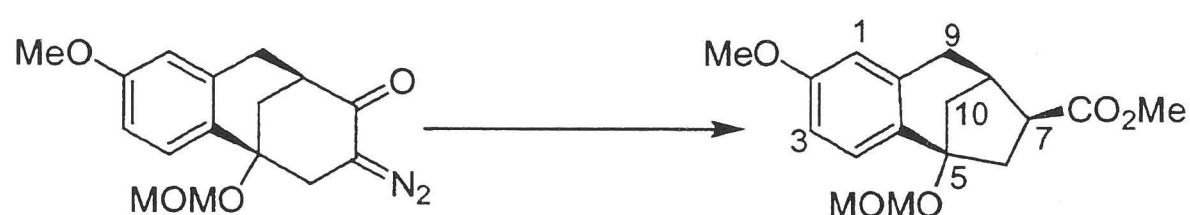
R_f: 0.52 EtOAc 75%, Pet. Sp. 25%

IR: (Neat) 2935, 2085, 1702, 1627, 1499 cm⁻¹

¹H NMR: (CDCl₃): 2.25 (ddd, 1H, *J*=12.8 Hz, *J*=4.4 Hz, *J*=1.8 Hz, H11) 2.45 (dt, 1H, *J*=12.8 Hz, *J*=2.5 Hz, H11) 2.74 (dd, 1H, *J*=12.7 Hz, *J*=2.8 Hz, H6) 2.91 (m, 1H, H9) 2.97 (d, 1H, *J*=17.0 Hz, H10) 3.11 (dd, 1H, *J*=16.8 Hz, *J*=5.8 Hz, H10) 3.27 (d, 1H, *J*=12.6 Hz, H6) 3.40 (s, 3H, OCH₂OCH₃) 3.76 (s, 3H, OMe) 4.55 (d, 1H, *J*=7.6 Hz, OCH₂OCH₃) 4.71 (d, 1H, *J*=7.2 Hz, OCH₂OCH₃) 6.56 (d, 1H, *J*=2.6 Hz, H1) 6.80 (dd, 1H, *J*=8.8 Hz, *J*=2.6 Hz, H3) 7.43 (d, 1H, *J*=8.7 Hz, H4)

¹³C NMR: (CDCl₃): 33.6 (CH₂), 34.6 (CH₂), 37.9 (CH₂), 42.2 (CH), 54.6 (CH₃), 55.0 (CH₃), 61.9 (C), 74.4 (C), 91.5 (CH₂), 112.2 (CH), 113.3 (CH), 126.4 (CH), 130.1 (C), 136.8 (C), 158.6 (C), 195.4 (C)

(5*SR*,7*SR*,8*RS*)-Methyl-6,7,8,9-tetrahydro-2-methoxy-5-methoxymethoxy-5,8-methano-5*H*-benzocycloheptene-7-carboxylate(43)



Diazoketone **53** (12 g) was dissolved in methanol (3 l) and the solution irradiated with a medium pressure mercury vapor lamp (450 watts) at 0°C until tlc analysis indicated that the starting material had been consumed (approx. 8 hours). Irradiation was stopped and the solvent removed *in vacuo* to yield the crude ester. The crude product was purified by column chromatography (ethyl acetate/petroleum spirit 3:1) to give the ester as a 6:1 mixture of 7-epimers (6.8 g, 61 % for the 3 steps).

R_f: 0.76 EtOAc 75%, Pet. Sp. 25%

IR: (Neat) 2948, 2840, 2135, 1739, 1609, 1578, 1496 cm⁻¹

¹H NMR: (CDCl₃): 2.06 (dd, 1H, *J*=10.8 Hz, *J*=1.4 Hz, H10), 2.23 (m, 2H, H6, H10), 2.42 (ddd, 1H, *J*=12.8 Hz, *J*=4.9 Hz, *J*=2.1 Hz, H6), 2.58 (d, 1H, *J*=17.3 Hz, H9), 2.98 (m, 2H, H8, H9), 3.27 (ddd, 1H, *J*=12.4 Hz, *J*=7.3 Hz, *J*=5.0 Hz, H7), 3.44 (s, 3H, OCH₂OCH₃), 3.62 (s, 3H, CO₂CH₃), 3.75 (s, 3H, OMe), 4.71 (d, 1H, *J*=6.9 Hz, OCH₂OCH₃), 4.80 (d, 1H, *J*=6.9 Hz, OCH₂OCH₃), 6.55 (d, 1H, *J*=2.6 Hz, H1), 6.71 (dd, 1H, *J*=8.5 Hz, *J*=2.6 Hz, H3), 7.24 (d, 1H, *J*=8.5 Hz, H4)

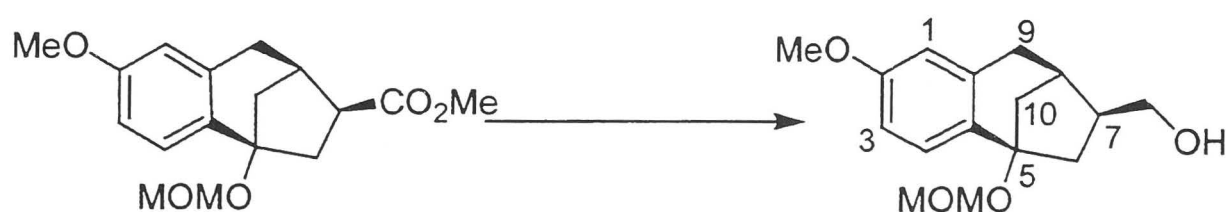
¹³C NMR: (CDCl₃): 33.6 (CH₂), 37.1 (CH), 40.4 (CH₂), 41.9 (CH₂), 44.0 (CH), 50.9 (CH₃), 54.4 (CH₃), 54.8 (CH₃), 83.0 (C), 92.4 (CH₂), 111.1 (CH), 113.0 (CH), 122.6 (CH), 134.8 (C), 135.8 (C), 157.7 (C), 173.2 (C)

MS (EI) m/z : 306 (M^+ , 57%), 261 (15), 245 (22), 219 (100), 201 (33), 189 (61), 187 (61), 175 (46), 159 (59), 148 (21), 128 (25), 115 (38), 103 (19), 84 (54)

HRMS m/z calc'd for $C_{17}H_{22}O_5$: 306.1467, found 306.1466

1H NMR (for minor *exo* isomer) ($CDCl_3$): 1.96 (dd, 1H, $J=11.0$ Hz, $J=1.5$ Hz, H10), 2.04-2.28 (m, 2H, H6, H10), 2.38 (dd, 1H, $J=12.0$ Hz, $J=7.9$ Hz, H6), 2.58 (t, 1H, $J=8.2$ Hz, H7), 2.71 (d, 1H, $J=17.0$ Hz, H9), 2.81 (m, 1H, H8), 3.09 (dd, 1H, $J=16.9$ Hz, $J=4.1$ Hz, H9), 3.44 (s, 3H, OCH_2OCH_3), 3.69 (s, 3H, CO_2CH_3), 3.76 (s, 3H, OMe), 4.71 (d, 1H, $J=6.9$ Hz, OCH_2OCH_3), 4.77 (d, 1H, $J=6.9$ Hz, OCH_2OCH_3), 6.62 (d, 1H, $J=2.6$ Hz, H1), 6.73 (dd, 1H, $J=8.6$ Hz, $J=2.6$ Hz, H3), 7.30 (d, 1H, $J=8.6$ Hz, H4)

(5*SR*,7*SR*,8*RS*)-6,7,8,9-Tetrahydro-2-methoxy-5-methoxymethoxy-5,8-methano-5*H*-benzocycloheptenyl-7-methanol (58)



Lithium aluminum hydride (1.1 g) was suspended in dry diethyl ether (500 ml) and the solution cooled to 0°C with an ice bath. The ester **43** (7.5 g) was dissolved in dry ether (100 ml) and this solution added dropwise to the cooled hydride suspension. The reaction was stirred for a further 2 h and then quenched with aqueous potassium hydrogen sulfate (1 M, 300 ml). The mixture was then extracted with ethyl acetate (3x 300 ml), the organic layers were combined and washed with water (400 ml), brine (400 ml) and then dried and evaporated *in vacuo*. The crude mixture was purified by column chromatography (ethyl acetate/petroleum spirit 3:1) to yield the pure alcohol as a clear oil (6.7 g, 98%).

R_f: 0.35 EtOAc 50%, Pet. Sp. 50%

IR: (Neat) 3428, 2940, 2839, 1608, 1577, 1495, 1465, 1444 cm⁻¹

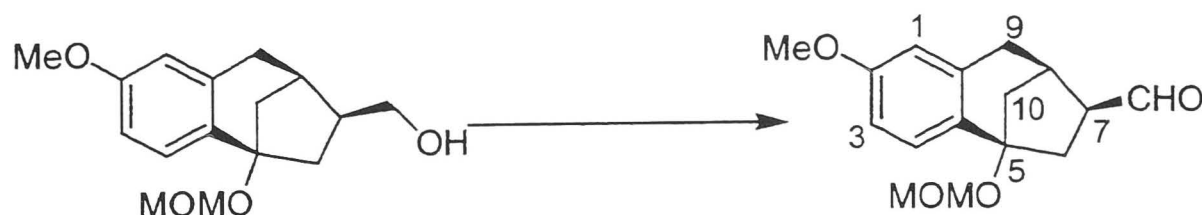
¹H NMR: (CDCl₃): 1.48 (ddd, 1H, *J*=12.5 Hz, *J*=4.4 Hz, *J*=2.2 Hz, H6), 2.08 (dd, 1H, *J*=10.8 Hz, *J*=1.9 Hz, H10), 2.19-2.27 (m, 2H, H6, H10), 2.55 (m, 1H, H7), 2.66 (m, 1H, H8), 2.84 (d, 1H, *J*=17.4 Hz, H9), 2.98 (dd, 1H, *J*=17.4 Hz, *J*=4.5 Hz, H9), 3.39-3.51 (m, 5H, CH₂OH, OCH₂OCH₃), 3.77 (s, 3H, OMe), 4.71 (d, 1H, *J*=6.8 Hz, OCH₂OCH₃), 4.78 (d, 1H, *J*=6.8 Hz, OCH₂OCH₃), 6.63 (d, 1H, *J*=2.5 Hz, H1), 6.70 (dd, 1H, *J*=8.5 Hz, *J*=2.6 Hz, H3), 7.23 (d, 1H, *J*=8.6 Hz, H4)

¹³C NMR: (CDCl₃): 32.5 (CH₂), 35.2 (CH), 40.1 (CH), 40.7 (CH₂), 43.9 (CH₂), 55.0 (CH₃), 55.3 (CH₃), 64.4 (CH₂), 83.5 (C), 92.8 (CH₂), 111.4 (CH), 113.3 (CH), 123.1 (CH), 136.2 (C), 137.0 (C), 158.0 (C)

MS (EI) *m/z*: 278 (M⁺, 34%), 233 (8), 219 (100), 189 (49), 187 (38), 175 (48), 159 (24), 115 (20)

HRMS *m/z* calc'd for C₁₆H₂₂O₄: 278.1518, found 278.1515

(5*SR*,7*SR*,8*RS*)-6,7,8,9-Tetrahydro-2-methoxy-5-methoxymethoxy-5,8-methano-5*H*-benzocycloheptene-7-carbaldehyde (57)



Triethylamine (11 ml), dimethyl sulfoxide (50 ml) and the alcohol 58 (5 g) were dissolved in dichloromethane (100 ml) and this solution cooled to 0°C.

Sulfur trioxide/pyridine complex (8.6 g) was then added to this solution in one portion and the reaction stirred for 50 min at 0°C. The solution was diluted with dichloromethane (300 ml) and washed with aqueous hydrochloric acid (1 M, 2x 200 ml), water (200 ml), brine (200 ml) and then dried and the solvent removed *in vacuo*. The crude product was purified by column chromatography (ethyl acetate/petroleum spirit 2:3) to give the aldehyde as a clear oil (4.7 g, 94%).

R_f: 0.42 (major), 0.54 (minor) EtOAc 40%, Pet. Sp. 60%

IR: (Neat) 2942, 2838, 1718, 1608, 1577, 1496, 1445 cm⁻¹

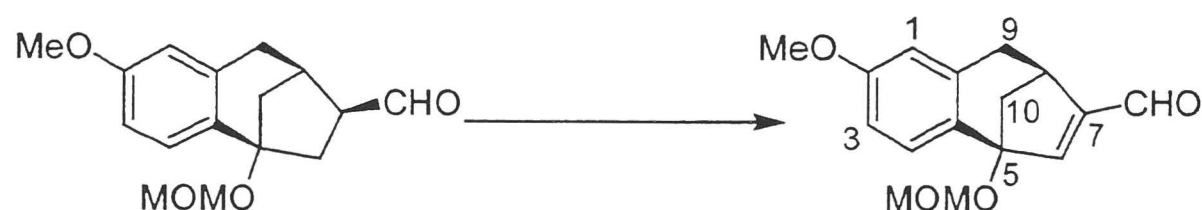
¹H NMR: (CDCl₃): 2.13 (dd, 1H, *J*=10.9 Hz, *J*=2.1 Hz, H6), 2.21-2.29 (m, 2H, H6, H10), 2.37 (ddd, 1H, *J*=13.2 Hz, *J*=3.7 Hz, *J*=2.1 Hz, H10), 2.78 (d, 1H, *J*=17.3 Hz, H9), 3.00-3.11 (m, 3H, H7, H8, H9), 3.45 (s, 3H, OCH₂OCH₃), 3.75 (s, 3H, OMe), 4.71 (d, 1H, *J*=6.9 Hz, OCH₂OCH₃), 4.80 (d, 1H, *J*=6.9 Hz, OCH₂OCH₃), 6.55 (d, 1H, *J*=2.6 Hz, H1), 6.74 (dd, 1H, *J*=8.5 Hz, *J*=2.6 Hz, H3), 7.29 (d, 1H, *J*=8.5 Hz, H4), 9.47 (s, 1H, CHO)

¹³C NMR: (CDCl₃): 33.9 (CH₂), 37.3 (CH), 41.1 (CH₂), 41.3 (CH₂), 50.3 (CH), 55.2 (CH₃), 55.6 (CH₃), 83.7 (C), 93.1 (CH₂), 112.4 (CH), 113.4 (CH), 123.7 (CH), 134.6 (C), 135.6 (C), 158.5 (C), 204.0 (CH)

MS (EI) *m/z*: 276(M⁺, 88%), 247 (54), 219 (100), 217 (80), 215 (54), 189 (54), 187 (66), 175 (68), 173 (71), 159 (47), 128 (32), 115 (42)

HRMS *m/z* calc'd for C₁₆H₂₀O₄: 276.1362, found 276.1360

(5*SR*,8*RS*)-8,9-Dihydro-2-methoxy-5-methoxymethoxy-5,8-methano-5*H*-benzocycloheptenyl-7-carbaldehyde (59)



The aldehyde **57** (4.7 g) and piperidine (5 ml) were dissolved in dichloromethane (400 ml) and phenylselenenyl chloride (6.6 g) was added in one portion. The reaction was stirred at room temperature for 4 hours and then diluted with dichloromethane (200 ml) and washed with aqueous hydrochloric acid (1 M, 2x 400 ml), water (400 ml), brine (400 ml) and then dried and the solvent removed *in vacuo*. The crude mixture was dissolved in tetrahydrofuran (300ml) and a solution of sodium periodate (24 g) in water (300 ml) was added slowly. The reaction was stirred vigorously for 3 h while additional water was added to dissolve any precipitate formed. The reaction was extracted with ethyl acetate (3x 300 ml), the organic layers were combined and washed with aqueous sodium hydroxide (2x 400 ml), water (400 ml), brine and then dried and evaporated *in vacuo*. The crude product was purified by column chromatography (ethyl acetate/petroleum spirit 2:3) to give the enal as a clear oil (3.9 g, 84%).

R_f: 0.74 EtOAc 50%, Pet. Sp. 50%

IR: (Neat) 2947, 2901, 2834, 1674, 1606, 1576, 1492, 1465, 1452, 1428 cm⁻¹

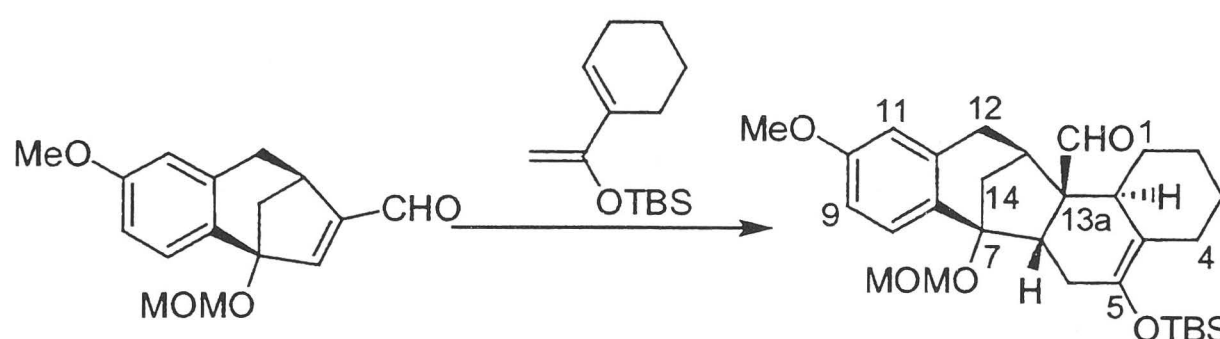
¹H NMR: (CDCl₃): 2.06 (d, 1H, *J*=10.1 Hz, H10), 2.61-2.66 (m, 2H, H9, H10), 3.08 (dd, 1H, *J*=17.9 Hz, *J*=4.8 Hz, H9), 3.47-3.52 (m, 4H, H8, OCH₂OCH₃), 3.76 (s, 3H, OMe), 4.87 (d, 1H, *J*=7.2 Hz, OCH₂OCH₃), 4.98 (d, 1H, *J*=7.2 Hz, OCH₂OCH₃), 6.61 (d, 1H, *J*=2.5 Hz, H1), 6.71 (dd, 1H, *J*=8.5 Hz, *J*=2.8 Hz, H3), 7.08 (s, 1H, H6), 7.43 (d, 1H, *J*=8.5 Hz, H4), 9.61 (s, 1H, CHO)

^{13}C NMR: (CDCl_3): 30.7 (CH_2), 35.1 (CH), 44.0 (CH_2), 55.0 (CH_3), 55.5 (CH_3), 86.4 (C), 92.2 (CH_2), 110.8 (CH), 115.0 (CH), 123.2 (CH), 131.7 (C), 135.1 (C), 143.1 (C), 157.5 (CH), 159.2 (C), 188.5 (CH)

MS (EI) m/z : 274 (M^+ , 15%), 246 (21), 201 (100), 159 (21)

HRMS m/z calc'd for MH^+ $\text{C}_{16}\text{H}_{19}\text{O}_4$: 275.1283, found 275.1281

(6a*SR*,7*SR*,13*RS*,13a*SR*,13b*RS*)-2,3,4,6,6a,7,12,13,13a,13b-Decahydro-5-*tert*-butyldimethylsilyloxy-10-methoxy-7-methoxymethoxy-7,13-methano-1*H*-benzo[4,5]cyclohepta[1,2-*a*]-naphthalene-13a-carbaldehyde (61)



The enal **59** (1.5 g), $\text{Yb}(\text{thd})_3$ (0.5 g) and diene **60** (6 g) were dissolved in 1,2-dichloroethane (120 ml) and the mixture heated under reflux overnight. The solvent was removed *in vacuo* and the crude product was purified by column chromatography (ethyl acetate/petroleum spirit/ triethylamine 15%:84%:1%) to give the Diels Alder adduct as a white solid (2.4 g, 86%).

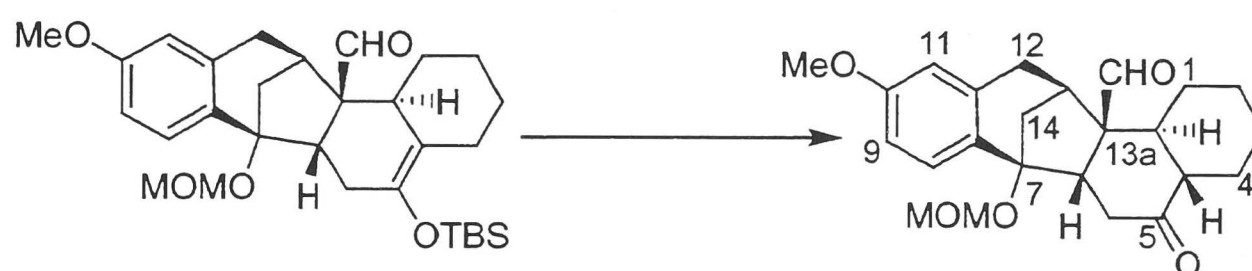
R_f : 0.55 EtOAc 15%, Pet. Sp. 84%, NEt_3 1%

^1H NMR: (CDCl_3): 0.07 (s, 3H, SiCH_3), 0.11 (s, 3H, SiCH_3), 0.94 (s, 9H, $\text{SiC}(\text{CH}_3)_3$), 1.21-1.78 (m, 5H), 1.82-1.90 (m, 2H), 2.01 (d, 1H, $J=11.1$ Hz), 2.11-2.43 (m, 4H), 2.54 (dd, 1H, $J=10.0$ Hz, $J=6.0$ Hz), 2.65-2.71 (m, 2H), 2.96 (dd, 1H, $J=17.5$ Hz, $J=3.9$ Hz, H12), 3.08 (d, 1H, $J=17.7$ Hz, H12), 3.45 (s, 3H, OCH_2OCH_3), 3.74 (s, 3H, OMe), 4.63 (d, 1H, $J=7.1$ Hz, OCH_2OCH_3), 4.70 (d,

1H, $J=7.1$ Hz, OCH_2OCH_3), 6.52 (d, 1H, $J=2.5$ Hz, H11), 6.70 (dd, 1H, $J=8.6$ Hz, $J=2.6$ Hz, H9), 7.23 (d, 1H, $J=8.5$ Hz, H8), 9.51 (s, 1H, CHO)

^{13}C NMR: (CDCl_3): -4.2 (CH_3), -4.0 (CH_3), 17.9 (C), 20.9 (CH_2), 21.1 (CH_2), 22.3 (CH_2), 23.3 (CH_2), 25.5 (CH_3), 25.7 (CH_3), 25.8 (CH_3), 30.7 (CH_2), 33.7 (CH_2), 37.5 (CH_2), 40.1 (CH), 43.6 (CH), 53.3 (CH), 54.9 (CH_3), 55.7 (CH_3), 61.9 (C), 84.5 (C), 92.9 (CH_2), 112.3 (CH), 113.2 (CH), 114.4 (C), 123.9 (CH), 135.6 (C), 136.5 (C), 143.2 (C), 158.4 (C), 205.1 (CH)

(4a*SR*,6a*SR*,7*SR*,13*RS*,13a*SR*,13b*SR*)-2,3,4,4a,5,6,6a,7,12,13,13a,13b-Dodecahydro-10-methoxy-7-methoxymethoxy-5-oxo-7,13-methano-1*H*-benzo[4,5]cyclohepta[1,2-*a*]-naphthalene-13a-carbaldehyde (63)



Silyl enol ether 61 (1 g) was dissolved in THF (150 ml) and the solution cooled to 0°C . A THF solution of TBAF (1 M, 2.3 ml) was added and the reaction stirred at 0°C for 1 hour. Water (150 ml) was added to the reaction mixture and the solution extracted with ethyl acetate (3x 200 ml). The organic layers were combined and washed with water (400 ml) and brine (300 ml), then dried and the solvent removed *in vacuo*. The crude product was purified by column chromatography (dichloromethane/ethyl acetate/petroleum spirit 4:1:2) to give the pure ketone as white crystals (0.66 g, 85%).

R_f : 0.55 DCM 55%, EtOAc 15%, Pet. Sp. 30%

IR: (Neat) 2926, 2847, 1706, 1687, 1610, 1573, 1493, 1447 cm^{-1}

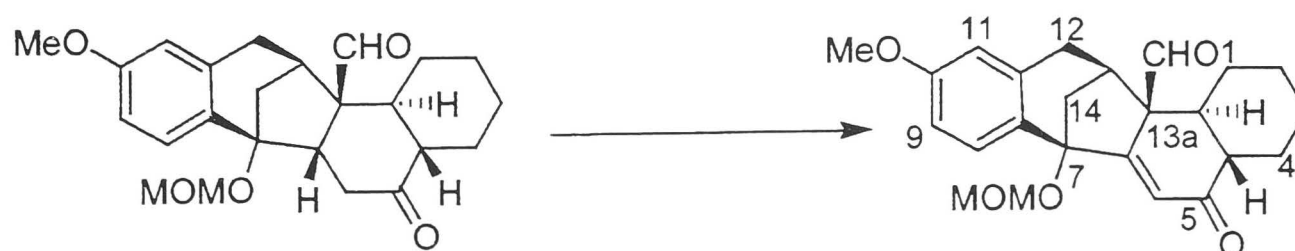
¹H NMR: (CDCl₃): 1.03-1.31 (m, 4H), 1.67 (td 1H, *J*=12.0 Hz, *J*=3.8 Hz), 1.76-1.93 (m, 3H), 2.07-2.23 (m, 3H), 2.42-2.56 (m, 2H), 2.66 (dd, 1H, *J*=14.6, Hz, *J*=5.4 Hz), 2.84-2.93 (m, 2H), 3.02 (d, 1H, *J*=17.5 Hz, H12), 3.11 (dd, 1H, *J*=17.6 Hz, *J*=3.5 Hz, H12), 3.40 (s, 3H, OCH₂OCH₃), 3.71 (s, 3H, OMe), 4.57 (d, 1H, *J*=7.0 Hz, OCH₂OCH₃), 4.66 (d, 1H, *J*=7.0 Hz, OCH₂OCH₃), 6.49 (d, 1H, *J*=2.5 Hz, H11), 6.68 (dd, 1H, *J*=8.7 Hz, *J*=2.5 Hz, H9), 7.18 (d, 1H, *J*=8.7 Hz, H8), 9.70 (s, 1H, CHO)

¹³C NMR: (CDCl₃): 25.8 (CH₂), 26.8 (CH₂), 28.2 (CH₂), 29.1 (CH₂), 33.7 (CH₂), 36.6 (CH₂), 38.5 (CH₂), 40.1 (CH), 46.2 (CH), 48.4 (CH), 48.5 (CH), 55.0 (CH₃), 55.8 (CH₃), 57.6 (C), 83.7 (C), 92.8 (CH₂), 112.6 (CH), 113.3 (CH), 124.3 (CH), 134.4 (C), 135.2 (C), 158.6 (C), 204.5 (CH), 213.6 (C)

MS (EI) *m/z*: 398 (M⁺ 14%), 369 (26), 219 (100), 189 (21), 135 (32), 159 (12)

HRMS *m/z* calc'd for C₂₄H₃₀O₅: 398.2093, found 398.2090

(4a*SR*,7*SR*,13*RS*,13a*SR*,13b*SR*)-2,3,4,4a,5,7,12,13,13a,13b-Decahydro-10-methoxy-7-methoxymethoxy-5-oxo-7,13-methano-1*H*-benzo[4,5]cyclohepta[1,2-*a*]-naphthalene-13a-carbaldehyde(64)



The ketone **63** (35 mg) was added to a freshly prepared solution of LDA (18 mg) in THF (3 ml) at -78°C, followed by TMSCl (14 μl). The resulting solution was stirred at -78°C for 1 hour and then quenched by the addition of a saturated NH₄Cl solution (3 ml). The aqueous layer was extracted with

ethyl acetate (3x 4 ml), the organic layers combined and washed with brine (6 ml), dried and evaporated *in vacuo*. The crude silyl enol ether (44 mg) was dissolved in DMSO (4 ml) and Pd(OAc)₂ (20 mg) was added and the resulting solution heated at 70°C overnight. The reaction mixture was diluted with water (8 ml) and extracted with ethyl acetate (3x 6 ml). The organic layers were combined, washed with water (2x 10 ml), brine (10 ml), dried and evaporated *in vacuo* to give the crude enone. The crude product was purified by column chromatography (dichloromethane/ethyl acetate/petroleum spirit 4:1:2) to give the pure enone (22 mg, 63%) and recovered starting material (12 mg, 34%).

R_f: 0.64 DCM 55%, EtOAc 15%, Pet. Sp. 30%

IR: (Neat) 2933, 2855, 1714, 1667, 1609, 1573, 1493, 1449 cm⁻¹

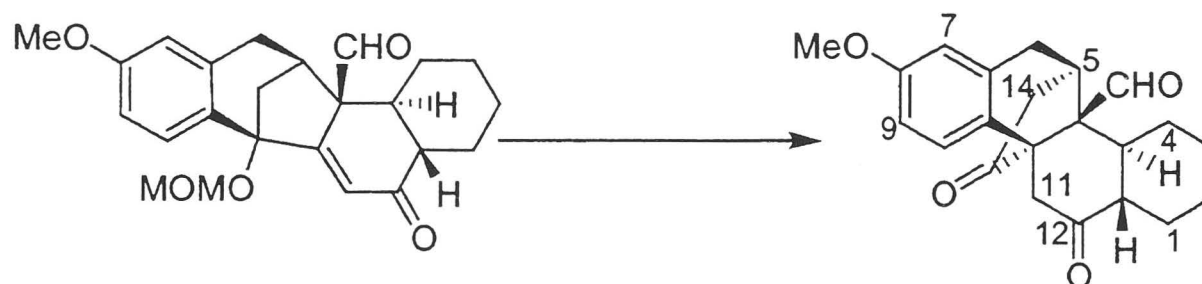
¹H NMR: (CDCl₃): 0.95-1.29 (m, 4H), 1.43 (m, 1H), 1.80-1.96 (m, 4H), 2.03 (d, 1H, *J*=12.9 Hz), 2.20-2.31 (m, 2H), 2.40 (d, 1H, *J*=13.0 Hz), 2.89 (m, 1H, H13), 3.02 (d, 1H, *J*=17.3 Hz, H12), 3.13 (dd, 1H, *J*=17.3 Hz, *J*=3.4 Hz, H12), 3.41 (s, 3H, OCH₂OCH₃), 3.75 (s, 3H, OMe), 4.74 (d, 1H, *J*=6.9 Hz, OCH₂OCH₃), 4.81 (d, 1H, *J*=6.9 Hz, OCH₂OCH₃), 6.11 (s, 1H, H6), 6.52 (d, 1H, *J*=2.6 Hz, H11), 6.73 (dd, 1H, *J*=8.7 Hz, *J*=2.6 Hz, H9), 7.30 (d, 1H, *J*=8.7 Hz, H8), 9.23 (s, 1H, CHO)

¹³C NMR: (CDCl₃): 25.9 (CH₂), 26.2 (CH₂), 27.6 (CH₂), 28.1 (CH₂), 34.9 (CH₂), 36.9 (CH), 40.2 (CH₂), 48.9 (CH), 50.9 (CH), 55.5 (CH₃), 56.2 (CH₃), 59.3 (C), 82.9 (C), 93.0 (CH₂), 113.5 (CH), 114.2 (CH), 116.8 (CH), 126.1 (CH), 129.7 (C), 135.8 (C), 159.7 (C), 171.8 (C), 199.8 (C), 201.6 (CH)

MS (EI) *m/z*: 396 (M⁺, 3%), 368 (45), 340 (52), 327 (100), 307 (36) 295 (31), 219 (20), 165 (19), 81 (22), 67 (32)

HRMS m/z calc'd for $M.Na^+ C_{24}H_{28}O_5Na$: 419.1834, found 419.1831

(4a*SR*,4b*SR*,5*SR*,10b*RS*,12a*SR*)-1,2,3,4,4a,4b,5,6,10b,11,12,12a-dodecahydro-12,13-dioxo-8-methoxy-5,10b-ethanochrysene-4b-carbaldehyde (66)



Enone 64 (20 mg) was dissolved in THF (3 ml) and MeOH (2 ml) and aqueous HCl (1 M, 0.5 ml) was added. The resulting solution was stirred at room temperature for 16 hours and then diluted with water (5 ml) and extracted with EtOAc (3x 10 ml). The organic layers were combined and washed with water (20 ml) and brine (20 ml), and then dried and evaporated *in vacuo* to give the crude dione. The crude product was purified by column chromatography (dichloromethane/ethyl acetate/petroleum spirit 4:1:2) to give the pure dione 66 (15 mg, 84%) as a white solid.

R_f: 0.56 EtOAc 50%, Pet. Sp. 50%

IR: (Neat) 2933, 2849, 1744, 1710, 1611, 1573, 1493, 1446 cm^{-1}

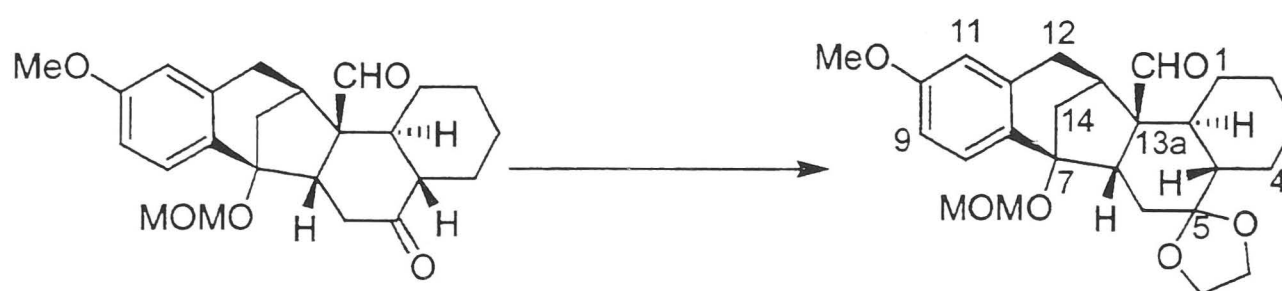
1H NMR: ($CDCl_3$): 1.06-1.34 (m, 5H), 1.45 (td, 1H, $J=12.2$ Hz, $J=2.9$ Hz), 1.74-1.85 (m, 2H), 2.05-2.25 (m, 3H), 2.71 (ddd, 1H, $J=19.3$ Hz, $J=7.7$ Hz, $J=1.3$ Hz, H13), 2.89 (dd, 1H, $J=18.0$ Hz, $J=1.8$ Hz, H11), 3.04 (dd, 1H, $J=14.8$ Hz, $J=0.6$ Hz, H6), 3.17 (m, 1H, H12), 3.40 (dd, 1H, $J=18.0$ Hz, $J=3.9$ Hz, H11), 3.55 (d, 1H, $J=14.8$ Hz, H6), 3.75 (s, 3H, OMe), 6.61 (d, 1H, $J=2.8$ Hz, H10), 6.78 (dd, 1H, $J=8.8$ Hz, $J=2.8$ Hz, H8), 6.99 (d, 1H, $J=8.9$ Hz, H7), 9.96 (s, 1H, CHO)

^{13}C NMR: (CDCl_3): 25.0 (CH_2), 25.8 (CH_2), 26.4 (CH_2), 27.6 (C), 31.0 (CH), 35.3 (CH_2), 40.9 (CH_2), 40.9 (CH_2), 45.0 (CH), 49.2 (CH), 55.6 (CH_3), 58.3 (C), 114.3 (CH), 114.7 (CH), 126.2 (CH), 127.5 (C), 133.9 (C), 159.5 (C), 202.8 (CH), 207.3 (C), 208.2 (C)

MS (EI) m/z : 352 (M^+ , 64%), 283 (100), 175 (26), 171 (32), 128 (17)

HRMS m/z calc'd for $\text{C}_{22}\text{H}_{24}\text{O}_4$: 352.1675, found 352.1679

(4a*SR*,6a*SR*,7*SR*,13*RS*,13a*SR*,13b*SR*)-2,3,4,6,6a,7,12,13,13a,13b-Decahydro-10-methoxy-7-methoxymethoxy-5,5-ethylenedioxy-7,13-methano-1*H*-benzo[4,5]cyclohepta[1,2-*a*]-naphthalene-13a-carbaldehyde (73)



Ketone **63** (200 mg) and pyridinium *p*-toluene sulfonate (200 mg) were dissolved in benzene (50 ml) and ethylene glycol (10 ml) and the mixture heated at reflux in a soxhlet apparatus charged with 3A molecular sieves. The reaction was followed by ^1H NMR, until all of the starting material had been consumed (approx. 2-3 days). The reaction mixture was diluted with water (100 ml), extracted with ethyl acetate (3x 100 ml), the organic layers combined and washed with dil. HCl (1M, 150 ml), water (150 ml), dil. NaOH (1M, 150 ml), water (150 ml) and brine, then dried and evaporated *in vacuo*. The crude product was purified by column chromatography (dichloromethane/ethyl acetate/petroleum spirit 4:1:4) to give the pure ketal (156 mg, 70%).

R_f: 0.50 EtOAc 10%, Pet. Sp. 45%, DCM 45%

IR: (Neat) 2937, 1714, 1609, 1577, 1495, 1464, 1447 cm⁻¹

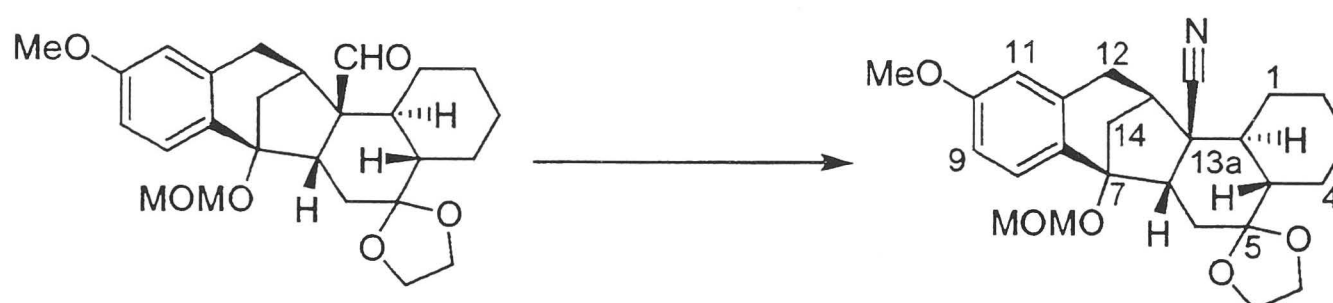
¹H NMR: (CDCl₃): 1.15-1.35 (m, 4H), 1.42-1.53 (m, 2H), 1.62-2.09 (m, 6H), 2.40-2.58 (m, 2H), 2.70 (m, 1H, H13) 2.82 (dd, 1H, *J*=13.8 Hz, *J*=5.0 Hz), 2.99 (m, 2H, H12) 3.44 (s, 3H, OCH₂OCH₃), 3.73 (s, 3H, OMe) 3.76-3.97 (m, 4H, OCH₂CH₂O), 4.61 (d, 1H, *J*=6.9 Hz, OCH₂OCH₃), 4.70 (d, 1H, *J*=6.9 Hz, OCH₂OCH₃), 6.49 (d, 1H, *J*=2.6 Hz, H11), 6.69 (dd, 1H, *J*=8.6 Hz, *J*=2.7 Hz, H9), 7.22 (d, 1H, *J*=8.6 Hz, H8), 9.57 (s, 1H, CHO)

¹³C NMR: (CDCl₃): 26.3 (CH₂), 26.8 (CH₂), 27.8 (CH₂), 28.8 (CH₂), 30.4 (CH₂), 33.9 (CH₂), 37.1 (CH₂), 40.2 (CH), 45.8 (CH), 46.4 (CH), 49.3 (CH), 55.0 (CH₃), 55.8 (CH₃), 57.5 (C), 63.4 (CH₂), 64.8 (CH₂), 83.8 (C), 92.8 (CH₂), 109.5 (C), 112.3 (CH), 113.1 (CH), 124.0 (CH), 135.0 (C), 136.1 (C), 158.3 (C), 205.8 (CH)

MS (EI) *m/z*: 442 (M⁺, 4%), 219 (100), 189 (50), 175 (48), 101 (60), 73 (50)

HRMS *m/z* calc'd for MH⁺ C₂₆H₃₅O₆: 443.2434, found 443.2422

(4a*SR*,6a*SR*,7*SR*,13*RS*,13a*SR*,13b*SR*)-2,3,4,6,6a,7,12,13,13a,13b-Decahydro-10-methoxy-7-methoxymethoxy-5,5-ethylenedioxy-7,13-methano-1*H*-benzo[4,5]cyclohepta[1,2-*a*]-naphthalene-13a-carbonitrile (71)



The aldehyde **73** (156 mg) and hydroxylamine hydrochloride (80 mg) were dissolved in pyridine (4 ml) and the solution heated at 100°C for 4 h. After this time the reaction was poured into EtOAc (15 ml) and the solution was brought to pH 5 with dil. HCl (1M). The organic layer was separated and washed with water (20 ml), sat. NH₄Cl solution (20 ml), water (20 ml), brine (20 ml) and was then dried and evaporated *in vacuo*. The crude oxime **75** was then dissolved in Ac₂O (5 ml) and heated at 100°C for 2 h and then cooled to room temperature. The reaction was quenched by the addition of dil NaOH (2M, 30 ml) followed by stirring for 1 h and then the solution was extracted with EtOAc (3x 20 ml), the organic layers were combined and washed with dil. NaOH (50 ml), water (50 ml) and brine (50 ml) and then dried and evaporated *in vacuo* to give the crude nitrile. This was purified by column chromatography (dichloromethane/ethyl acetate/petroleum spirit 4:1:2) to give the pure nitrile as white crystals (67 mg, 43 %).

R_f: 0.38 EtOAc 50%, Pet. Sp. 50%

IR: (Neat) 2937, 2882, 2853, 2225, 1609, 1572, 1495, 1466, 1447 cm⁻¹

¹H NMR: (CDCl₃): 1.19-1.32 (m, 3H), 1.37-1.50 (m, 2H), 1.59 (t, 1H, *J*=14.0 Hz), 1.72-2.01 (m, 6H), 2.07 (dd, 1H, *J*=11.7 Hz, *J*=1.0 Hz, H14), 2.30 (dd, 1H,

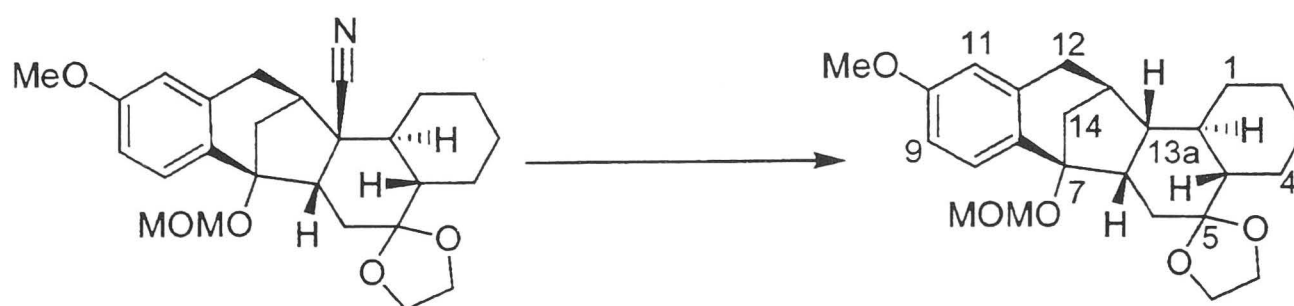
$J=11.7$ Hz, $J=5.3$ Hz, H14), 2.55 (m, 1H, H13), 2.71 (ddd, 1H, $J=13.8$ Hz, $J=5.1$ Hz, $J=1.2$ Hz, H6a), 3.13 (m, 2H,), 3.42 (s, 3H, OCH₂OCH₃), 3.77 (s, 3H, OMe), 3.76-3.87 (m, 2H, OCH₂CH₂O), 3.93-4.00 (m, 2H, OCH₂CH₂O), 4.59 (d, 1H, $J=7.0$ Hz, OCH₂OCH₃), 4.70 (d, 1H, $J=7.0$ Hz, OCH₂OCH₃), 6.68 (d, 1H, $J=2.5$ Hz, H11), 6.73 (dd, 1H, $J=8.5$ Hz, $J=2.6$ Hz, H9), 7.22 (d, 1H, $J=8.5$ Hz, H8)

¹³C NMR: (CDCl₃): 25.7 (CH₂), 25.8 (CH₂), 26.7 (CH₂), 29.5 (CH₂), 30.8 (CH₂), 35.2 (CH₂), 36.7 (CH₂), 39.8 (CH), 42.6 (CH), 46.1 (CH), 47.2 (C), 54.8 (CH), 55.2 (CH₃), 55.9 (CH₃), 63.6 (CH₂), 65.2 (CH₂), 83.8 (C), 92.9 (CH₂), 109.1 (C), 112.6 (CH), 113.6 (CH), 122.1 (C), 124.1 (CH), 135.3 (C), 135.3 (C), 158.8 (C)

MS (EI) m/z : 439 (M⁺, 1.4%), 394 (2), 378 (2), 268 (18), 219 (100), 189 (15)

HRMS m/z calc'd for M.H⁺ C₂₆H₃₄NO₅: 440.2437, found 440.2438

(4a*SR*,6a*SR*,7*SR*,13*RS*,13a*RS*,13b*RS*)-2,3,4,4a,5,6,6a,7,12,13,13a,13b-Dodecahydro-10-methoxy-7-methoxymethoxy-5,5-ethylenedioxy-7,13-methano-1*H*-benzo[4,5]cyclohepta[1,2-*a*]-naphthalene (76)



Lithium metal (5 mg) was added in one portion to freshly distilled ammonia (25 ml) at -78°C and allowed to dissolve. The nitrile **71** (25 mg) was dissolved in THF (5 ml) and this solution was added to the stirred lithium solution. This was then allowed to warm to -33°C over 2 hours. Solid ammonium acetate (100 mg) was added in one portion, after which the blue

colour faded immediately. The ammonia was allowed to evaporate and the resulting solution was diluted with ethyl acetate (20 ml) and was washed with water (20 ml) and brine (20 ml). The organic layer was then dried and the solvent removed *in vacuo* to give the crude compound. This was purified by column chromatography (dichloromethane/ethyl acetate/ petroleum spirit 4:1:4) to give the pure compound 76 as a white solid (16 mg, 68%).

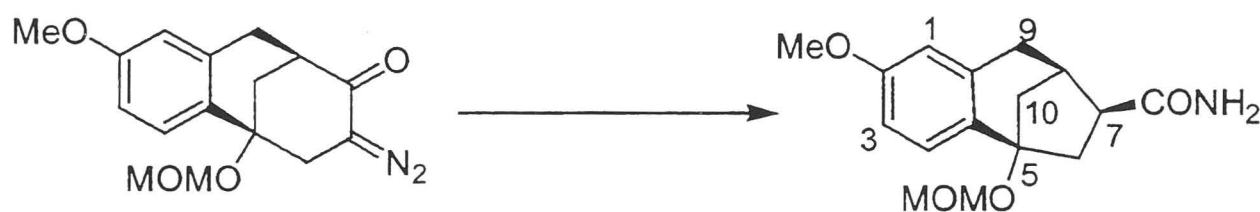
R_f: 0.50 DCM 45%, EtOAc 10%, Pet. Sp. 45%

IR: (Neat) 2928, 1607, 1494, 1447 cm⁻¹

¹H NMR: (CDCl₃): 0.84 (m, 1H), 1.16-1.38 (m, 7H), 1.51-1.85 (m, 5H), 1.94-2.06 (m, 2H), 2.19-2.27 (m, 2H) 2.57 (d, 1H,), 3.04 (d, 1H,), 3.42 (s, 3H, OCH₂OCH₃), 3.69-3.87 (m, 2H, OCH₂CH₂O), 3.77 (s, 3H, OMe), 3.92-4.03 (m, 2H, OCH₂CH₂O), 4.61 (d, 1H, J=6.6 Hz, OCH₂OCH₃), 4.68 (d, 1H, J=6.7 Hz, OCH₂OCH₃), 6.61 (d, 1H, J=2.4 Hz, H11), 6.70 (dd, 1H, J=8.5 Hz, J=2.4 Hz, H9), 7.26 (d, 1H, J=8.4 Hz, H8)

¹³C NMR: (CDCl₃): 25.6 (CH₂), 26.2 (CH₂), 26.6 (CH₂), 32.7 (CH₂), 34.1 (CH₂), 35.3 (CH₂), 38.2 (CH), 39.9 (CH), 40.7 (CH₂), 47.6 (CH), 48.4 (CH), 49.0 (CH), 55.5 (CH₃), 56.0 (CH₃), 63.7 (CH₂), 65.6 (CH₂), 85.4 (C), 93.3 (CH₂), 111.3 (C), 111.9 (CH), 114.2 (CH), 124.6 (CH), 137.2 (C), 137.5 (C), 158.6 (C)

(5*SR*,7*SR*,8*RS*)-6,7,8,9-Tetrahydro-2-methoxy-5-methoxymethoxy-5,8-methano-5*H*-benzocycloheptene-7-carboxamide (79)



Diazoketone **53** (12 g) was dissolved in THF (3 l) and hexamethyldisilazane (300 ml) and the solution irradiated with a medium pressure mercury vapor lamp (450 watts) until tlc analysis indicated that all of the starting material had been consumed (approx. 6 hours). Irradiation was stopped and the solvent removed *in vacuo*. The residue was dissolved in ethyl acetate (500 ml) and stirred with dil. HCl (2 M, 1 l) for 20 minutes. The solution was extracted with ethyl acetate (3x 300 ml), the organic layers combined and washed with dil. NaOH solution (1 M, 500 ml), water (800 ml) and brine (800 ml) and then dried and evaporated *in vacuo* to give the crude amide. This was purified by gradient column chromatography (ethyl acetate 100% to ethyl acetate/methanol 95%: 5%) to give the pure amide (7.9 g, 68%).

R_f: 0.20 EtOAc

IR: (Neat) 3336, 3200, 2941, 2247, 1651, 1609, 1494 cm⁻¹

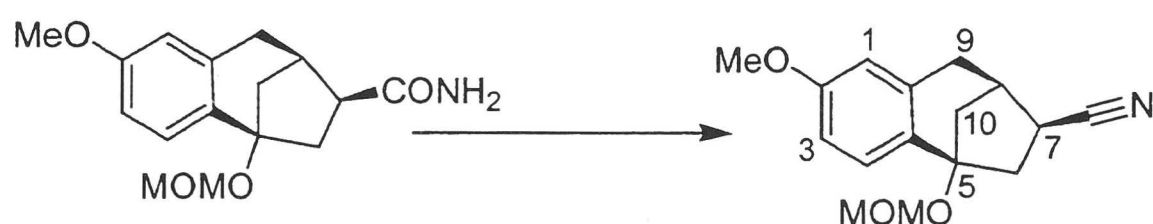
¹H NMR: (CDCl₃): 2.12-2.25 (m, 3H, H10, H6) 2.30 (t, 1H, *J*=13.0 Hz, H6) 2.81 (d, 1H, *J*=17.6 Hz, H9) 2.90 (m, 1H, H8) 3.01 (dd, 1H, *J*=17.6 Hz, *J*=4.0 Hz, H9) 3.20 (m, 1H, H7) 3.45 (s, 3H, OCH₂OCH₃) 3.75 (s, 3H, OMe) 4.72 (d, 1H, *J*=7.0 Hz, OCH₂OCH₃) 4.79 (d, 1H, *J*=7.0 Hz, OCH₂OCH₃) 5.26 (s, 1H, NH) 5.54 (s, 1H, NH) 6.59 (d, 1H, *J*=2.6 Hz, H1) 6.71 (dd, 1H, *J*=8.5 Hz, *J*=2.6 Hz, H3) 7.26 (d, 1H, *J*=8.5 Hz, H4)

^{13}C NMR: (CDCl_3): 33.0 (CH_2), 37.5 (CH), 40.5 (CH_2), 41.8 (CH_2), 45.2 (CH), 54.7 (CH_3), 55.1 (CH_3), 83.3 (C), 92.5 (CH_2), 111.0 (CH), 113.1 (CH), 122.5 (CH), 135.5 (C), 136.0 (C), 157.7 (C), 175.1 (C)

MS (EI) m/z : 291(M^+ , 62%), 246 (19), 229 (49), 219 (92), 187 (88), 175 (100), 159 (59), 147 (18), 128 (23), 115 (39), 103 (15), 91 (18), 72 (43)

HRMS m/z calc'd for $\text{C}_{16}\text{H}_{21}\text{NO}_4$: 291.1471, found 291.1473

(5*SR*,7*SR*,8*RS*)-6,7,8,9-Tetrahydro-2-methoxy-5-methoxymethoxy-5,8-methano-5*H*-benzocycloheptene-7-carbonitrile (78)



Amide 79 (6.3 g) and triethylamine (6.2 ml) were dissolved in DCM (100 ml) and the solution cooled to 0°C . Trichloroacetylchloride (2.8 ml) was added dropwise to the cooled solution and the solution was then stirred for an 5 minutes. The reaction mixture was diluted with DCM (100 ml) and washed with dil. NaOH (1M, 100 ml), water (200 ml), dil. HCl (100 ml), water (200 ml), brine (200 ml) and then dried and evaporated *in vacuo* to give the crude nitrile. The crude product was purified by column chromatography (ethyl acetate/petroleum spirit 1:1) to give the nitrile (5.8 g, 98%) as a 1:6 *exo*: *endo* mixture of diastereoisomers at the α carbon.

R_f : 0.57 (major), 0.71 (minor) EtOAc 50%, Pet. Sp. 50%

IR: (Neat) 2946, 2839, 2237, 1608, 1577, 1495, 1445 cm^{-1}

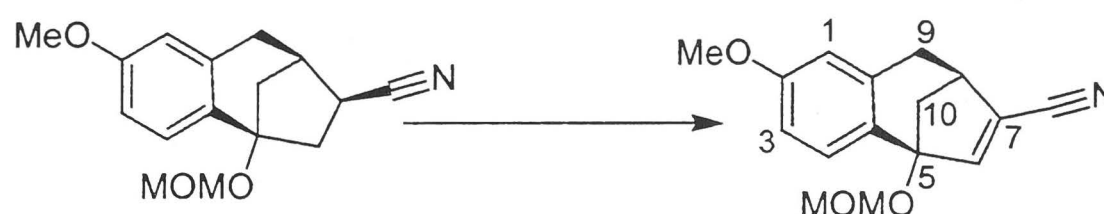
¹H NMR: (CDCl₃): 2.03-2.17 (m, 3H, H6, H10) 2.46 (t, 1H, *J*=12.6 Hz, H6) 2.81 (m, 1H, H8) 3.10 (m, 2H, H9) 3.24 (m, 1H, H7) 3.38 (s, 3H, OCH₂OCH₃) 3.74 (s, 3H, OMe) 4.65 (d, 1H, *J*=7.0 Hz, OCH₂OCH₃) 4.74 (d, 1H, *J*=7.0 Hz, OCH₂OCH₃) 6.71 (m, 2H, H1, H3) 7.23 (d, 1H, *J*=8.5 Hz, H4)

¹³C NMR: (CDCl₃): 28.2 (CH), 34.6 (CH₂), 36.0 (CH), 38.9 (CH₂), 45.2 (CH₂), 54.8 (CH₃), 55.3 (CH₃), 82.6 (C), 92.7 (CH₂), 112.3 (CH), 113.6 (CH), 121.0(C), 123.3 (CH), 134.2(C), 134.7(C), 158.6(C)

MS (EI) *m/z* 273 (M⁺, 67%), 228 (9), 219 (100), 189 (61), 175 (43), 160 (53), 146 (18), 128 (14), 115 (35), 77 (18)

HRMS *m/z* calc'd for C₁₆H₁₉NO₃: 273.1365, found 273.1362

(5*SR*,8*RS*)-8,9-Dihydro-2-methoxy-5-methoxymethoxy-5,8-methano-5*H*-benzocycloheptenyl-7-carbonitrile (81)



To a stirred, freshly made solution of LDA in THF (0.14 M, 100 ml) at 0°C was added potassium *tert*-butoxide (2.2 g). When the potassium *tert*-butoxide had dissolved, a solution of the nitrile 78 (1.5 g) in THF (50 ml) was added and the solution stirred for 10 minutes. After this time, diphenyl diselenide (6.9 g) was added and the solution stirred for 1.5 hours. The reaction was then quenched by the addition of water (100 ml) and diluted with ethyl acetate (300 ml). The organic layer was then separated and washed with aqueous HCl (1 M, 2x300 ml) and brine. The organic layer was then cooled with stirring to 0°C and hydrogen peroxide (30%w/v, 50 ml)

was added dropwise. When the addition of hydrogen peroxide was complete the solution was allowed to warm to room temperature for 2 hours. After this time the solution was washed with aqueous sodium hydroxide (1 M, 2x300 ml), water (300 ml) and brine (300 ml) and then dried and evaporated *in vacuo*. The residue was purified by column chromatography (ethyl acetate/petroleum spirit 1:3) to give the alkene (1.1 g, 74%) as an oil.

R_f: 0.26 EtOAc 25%, Pet. Sp. 75%

IR: (Neat) 2948, 2900, 2835, 2218, 1606, 1576, 1492, 1465, 1427 cm⁻¹

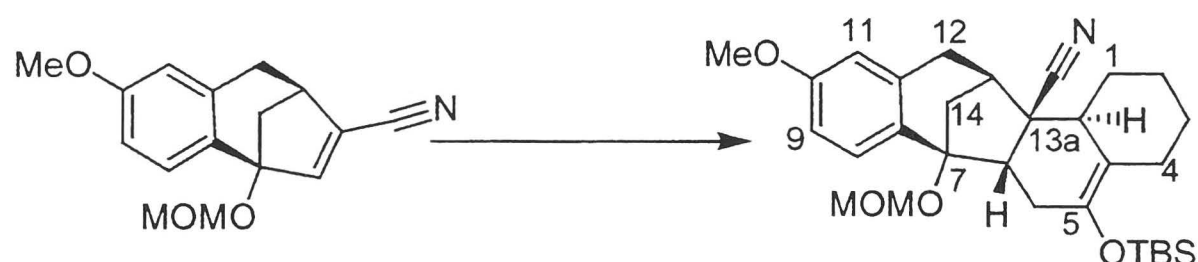
¹H NMR: (CDCl₃): 2.02 (d, 1H, *J*=10.3 Hz, H10) 2.62 (ddd, 1H, *J*=10.3 Hz, *J*=5.7 Hz, *J*=1.2 Hz, H10) 2.72 (d, 1H, *J*=17.9 Hz, H9) 3.08 (dd, 1H, *J*=17.7 Hz, *J*=4.8 Hz, H9), 3.26 (m, 1H, H8) 3.45 (s, 3H, OCH₂OCH₃) 3.74 (s, 3H, OMe) 4.80 (d, 1H, *J*=7.2 Hz, OCH₂OCH₃) 4.90 (d, 1H, *J*=7.2 Hz, OCH₂OCH₃) 6.64 (d, 1H, *J*=2.5 Hz, H1) 6.71 (dd, 1H, *J*=8.5 Hz, *J*=2.7 Hz, H3) 6.88 (d, 1H, *J*=0.8 Hz, H6) 7.39 (d, 1H, *J*=8.5 Hz, H4)

¹³C NMR: (CDCl₃): 30.0 (CH₂), 40.7 (CH), 43.4 (CH₂), 54.8 (CH₃), 55.3 (CH₃), 85.9 (C), 92.0 (CH₂), 110.9 (CH), 112.4 (C), 115.0 (CH), 115.4 (C), 123.1 (CH), 131.4 (C), 133.7 (C), 155.6 (CH), 159.4 (C)

MS (EI) *m/z*: 271 (M⁺, 26%), 239 (49) 210 (23) 198 (100) 184 (30) 169 (20) 153 (13) 140 (24) 127 (12) 115 (16) 84 (14) 63 (11)

HRMS *m/z* calc'd for C₁₆H₁₇NO₃: 271.1208, found 271.1208

(6a*SR*,7*SR*,13*RS*,13a*SR*,13b*RS*)-2,3,4,6,6a,7,12,13,13a,13b-Decahydro-5-*tert*-butyldimethylsilyloxy-10-methoxy-7-methoxymethoxy-7,13-methano-1*H*-benzo[4,5]cyclohepta[1,2-*a*]-naphthalene-13a-carbonitrile (82)



The alkene **81** (5.2 g) and Yb(thd)₃ (2.5 g) were dissolved in diene **60** (20 ml) and the mixture heated at 110°C for 3 days. The crude product was purified by column chromatography (ethyl acetate/petroleum spirit/ triethylamine 20%:79%:1%) to give the Diels Alder adduct as a white solid (8.5 g, 87%)

R_f: 0.38 EtOAc 20%, Pet. Sp. 79%, NEt₃ 1%

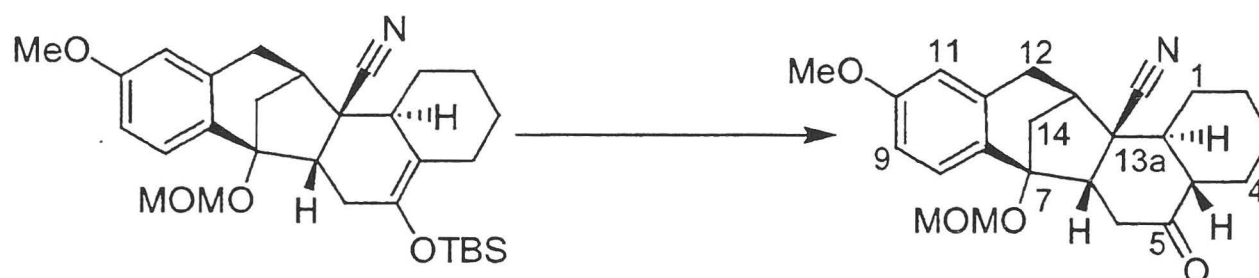
¹H NMR: (CDCl₃): 0.11 (s, 3H, SiCH₃) 0.12 (s, 3H, SiCH₃) 0.95 (s, 9H, SiC(CH₃)₃) 1.37 (m, 1H) 1.56 (m, 2H) 1.81 (m, 3H) 2.03-2.41 (m, 7H) 2.56 (m, 1H) 2.62 (dd, 1H *J*=11.0 Hz, *J*=6.8 Hz,) 3.11 (s, 2H, H₁₂) 3.42 (s, 3H, OCH₂OCH₃) 3.76 (s, 3H, OMe) 4.62 (d, 1H, *J*=7.1 Hz, OCH₂OCH₃) 4.71 (d, 1H, *J*=7.1 Hz, OCH₂OCH₃) 6.69 (d, 1H, *J*=2.5 Hz, H₁₁) 6.73 (dd, 1H, *J*=8.5 Hz, *J*=2.6 Hz, H₉) 7.23 (d, 1H, *J*=8.5 Hz, H₈)

¹³C NMR: (CDCl₃): -4.2 (CH₃), -4.1 (CH₃), 17.9 (C), 20.8 (CH₂), 21.4 (CH₂), 25.0 (CH₂), 25.6 (3xCH₃), 30.4 (CH₂), 35.4 (CH₂), 36.1 (CH₂), 39.9 (CH), 41.6 (CH), 50.9 (CH), 54.9 (CH₃), 55.7 (CH₃), 60.2 (CH), 84.2 (C), 92.8 (CH₂), 112.6 (CH), 113.6 (CH), 114.2 (C), 122.9 (C), 123.6 (CH), 135.2 (C), 135.9 (C), 143.9 (C), 158.8 (C)

MS (EI) *m/z*: 509 (M⁺, 40%), 464 (12), 438 (6), 238 (14), 219 (19), 182 (100), 73 (43)

HRMS m/z calc'd for $C_{30}H_{43}NO_4Si$: 509.2961, found 509.2967

(4a*SR*,6a*SR*,7*SR*,13*RS*,13a*SR*,13b*SR*)-2,3,4,4a,5,6,6a,7,12,13,13a,13b-
Dodecahydro-10-methoxy-7-methoxymethoxy-5-oxo-7,13-methano-1*H*-
benzo[4,5]cyclohepta[1,2-*a*]-naphthalene-13a-carbonitrile (84)



Silyl enol ether **82** (2.6 g) was dissolved in THF (200 ml) and the solution cooled to 0°C. A THF solution of TBAF (1 M, 6.0 ml) was added and the reaction stirred at 0°C for 1 hour. Water (200 ml) was added to the reaction and the solution extracted with ethyl acetate (3x 200 ml). The organic layers were combined and washed with water (500 ml) and brine (500 ml), then dried and the solvent removed *in vacuo*. The crude product was purified by column chromatography (dichloromethane/ethyl acetate/petroleum spirit 4:1:2) to give the pure ketone as white crystals (1.5 g, 74%)

R_f : 0.55 EtOAc 50%, Pet. Sp. 50%

m.p. 190°C

IR: (Neat) 2931, 2857, 2229, 1713, 1609, 1577, 1496 cm^{-1}

1H NMR: ($CDCl_3$): 1.05-1.19 (m, 1H), 1.22-1.37 (m, 2H), 1.47-1.61 (m, 1H), 1.72-2.06 (m, 5H), 2.18 (d, 1H $J=12.0$ Hz), 2.28-2.32 (m, 1H), 2.37-2.50 (m, 2H), 2.64-2.78 (m, 3H), 3.13 (d, 1H $J=17.3$ Hz, H12), 3.22 (dd, 1H $J=17.4$ Hz, $J=4.0$ Hz, H12), 3.41 (s, 3H, OCH_2OCH_3), 3.78 (s, 3H, OMe), 4.59 (d, 1H, $J=7.2$ Hz,

OCH₂OCH₃), 4.70 (d, 1H, $J=7.2$ Hz, OCH₂OCH₃), 6.70 (d, 1H, $J=2.5$ Hz, H11), 6.75 (dd, 1H, $J=8.5$ Hz, $J=2.7$ Hz, H9), 7.22(d, 1H, $J=8.6$ Hz, H8)

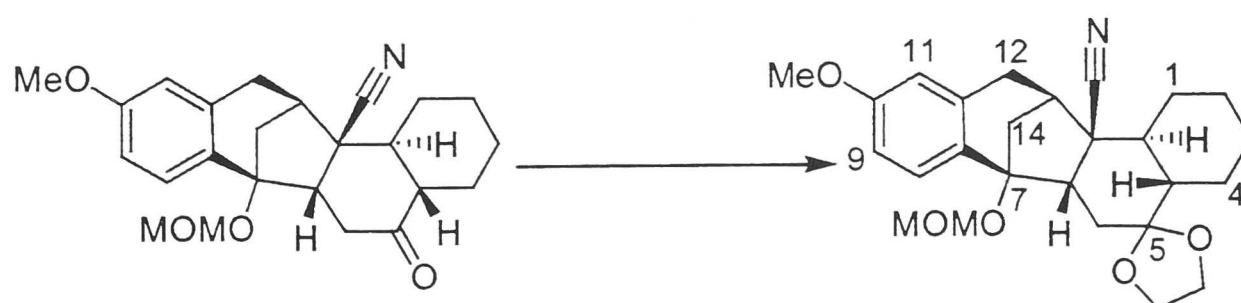
¹³C NMR: (CDCl₃): 25.4 (CH₂), 25.5 (CH₂), 28.3 (CH₂), 28.8 (CH₂), 34.7 (CH₂), 36.6 (CH₂), 38.0 (CH₂), 40.1 (CH), 43.1 (CH), 44.9 (CH), 47.3 (C), 48.8 (CH), 55.1 (CH₃), 56.0 (CH₃), 83.8 (C), 92.9 (CH₂), 112.9 (CH), 113.6 (CH), 121.5 (C), 124.2(CH), 134.5 (C), 135.0 (C), 159.1 (C), 211.8 (C)

MS (EI) m/z : 395 (M⁺, 21%), 334 (7), 282 (7), 219 (100), 189 (44), 175 (29), 160 (31), 147 (17), 131 (6), 115 (11), 91 (9)

HRMS m/z calc'd for C₂₄H₂₉NO₄: 395.2097 found: 395.2097

Analysis calc'd for C₂₄H₂₉NO₄: C 72.89, H 7.39, N 3.54 found: C73.07, H 7.25, N 3.40

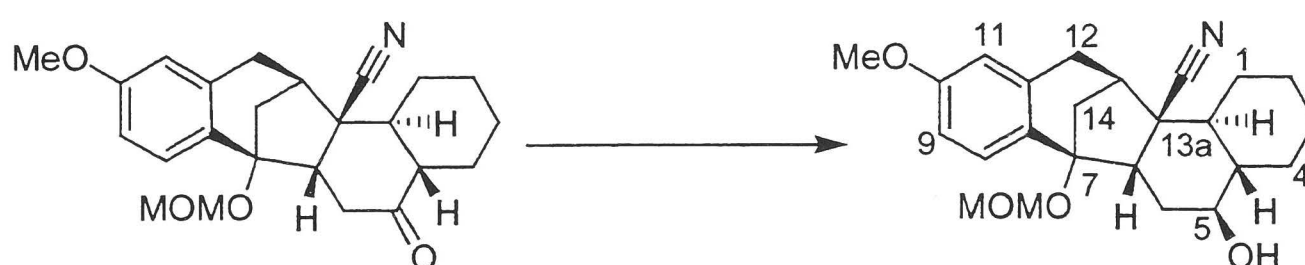
(4aSR,6aSR,7SR,13RS,13aSR,13bSR)-2,3,4,a4,5,6,6a,7,12,13,13a,13b-Dodecahydro-10-methoxy-7-methoxymethoxy-5,5-ethylenedioxy-7,13-methano-1H-benzo[4,5]cyclohepta[1,2-a]naphthalene-13a-carbonitrile (71)



The ketone **84** (200 mg) was dissolved in benzene (25 ml) and ethylene glycol (5 ml) and pyridinium tosylate (100 mg) were added. This solution was heated at reflux in a soxhlet apparatus charged with 3A molecular sieves. The reaction was followed by ¹HNMR, until all of the starting material had been consumed (approx. 2-3 days). The reaction mixture was

diluted with water (50 ml), extracted with ethyl acetate (3x 50 ml), the organic layers combined and washed with dil. HCl (1M, 100 ml), water (100 ml), dil. NaOH (1M, 100 ml), water (100 ml) and brine, then dried and evaporated *in vacuo*. The crude product was purified by column chromatography (ethyl acetate/petroleum spirit 1:1) to give the pure ketal (150 mg, 65%), which was identical to that obtained from the aldehyde.

(4aSR,5SR,6aSR,7SR,13RS,13aSR,13bSR)-2,3,4,4a,5,6,6a,7,12,13,13a,13b-Dodecahydro-10-methoxy-7-methoxymethoxy-5-hydroxy-7,13-methano-1H-benzo[4,5]cyclohepta[1,2-a]naphthalene-13a-carbonitrile (85)



Lithium aluminum hydride (150 mg) was suspended in dry diethyl ether (250 ml) and the solution cooled to -78°C with a dry ice/acetone bath. The ketone **84** (1.5 g) was dissolved in dry THF (50 ml) and this solution added dropwise to the cooled hydride suspension. The reaction was stirred for 5 minutes and then quenched with aqueous potassium hydrogen sulfate (1 M, 200 ml). The mixture was then extracted with ethyl acetate (3x 200 ml), the organic layers were combined and washed with water (400 ml), brine (400 ml) and then dried and evaporated *in vacuo* to give the crude product as a 9:1 mixture of 5-epimers (1.4 g, 94%).

R_f: 0.41 EtOAc 50%, Pet. Sp. 50%

IR: (Neat) 3480, 2930, 2856, 2229, 1609, 1577, 1495, 1464, 1448 cm^{-1}

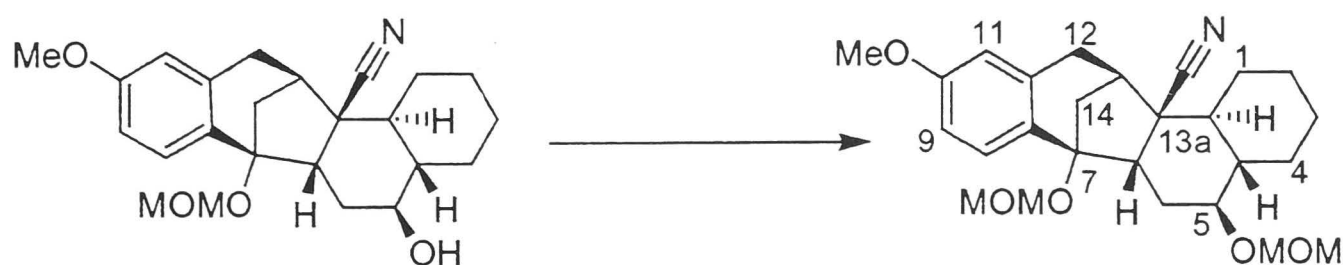
^1H NMR: (CDCl_3): 1.04-1.49 (m, 6H), 1.59 (m, 1H), 1.72-2.08 (m, 7H), 2.28 (dd, 1H, $J=11.7$ Hz, $J=5.3$ Hz), 2.53 (m, 1H, H13), 2.84 (dd, 1H, $J=13.2$ Hz, $J=4.8$ Hz), 3.12 (m, 2H, H12), 3.40 (s, 3H, OCH_2OCH_3), 3.70 (m, 1H, H5), 3.76 (s, 3H, OMe), 4.58 (d, 1H, $J=7.0$ Hz, OCH_2OCH_3), 4.68 (d, 1H, $J=7.0$ Hz, OCH_2OCH_3), 6.70 (m, 2H, H9, H11), 7.21 (d, 1H, $J=8.5$ Hz, H8)

^{13}C NMR: (CDCl_3): 26.1 (CH_2), 26.3 (CH_2), 28.7 (CH_2), 29.1 (CH_2), 33.7 (CH_2), 35.1 (CH_2), 36.6 (CH_2), 39.7 (CH), 42.1 (CH), 44.9 (CH), 47.2 (C), 52.9 (CH), 55.1 (CH_3), 55.8 (CH_3), 71.7 (CH), 83.8 (C), 92.9 (CH_2), 112.6 (CH), 113.5 (CH), 122.3 (C), 124.0 (CH), 135.2 (C), 135.6 (C), 158.7 (C)

MS (EI) m/z : 397 (M^+ 8%), 336 (4), 266 (6), 219 (100), 189 (39), 175 (31), 159 (22), 147 (12), 91 (8), 75 (12)

HRMS m/z calc'd for $\text{C}_{24}\text{H}_{31}\text{NO}_4$: 397.2253, found 397.2255

(4aSR,5SR,6aSR,7SR,13RS,13aSR,13bSR)-2,3,4,4a,5,6,6a,7,12,13,13a,13b-Dodecahydro-10-methoxy-5,7-bismethoxymethoxy-7,13-methano-1H-benzo[4,5]cyclohepta[1,2-a]naphthalene-13a-carbonitrile (86)



Compound 85 (1.4 g), DIPEA (1.3 ml) and DMAP (140 mg) were dissolved in dichloromethane (200 ml) and the solution cooled to 0°C with an ice bath. MOM chloride (1 ml) was added dropwise to the cooled solution and after the addition was complete the ice bath was removed and the reaction stirred for 16 h at room temperature. Excess MOM chloride was quenched by the addition of aqueous sodium hydroxide solution (0.5 M, 100 ml) followed by

stirring for 1 h at room temperature. The mixture was diluted with dichloromethane (200 ml), washed with water (300 ml), aqueous HCl (1 M, 300 ml), water (300 ml) and brine (300 ml). The organic layer was then dried and the solvent removed *in vacuo* to give the protected compound as an oil that solidified on standing (1.5 g, 96%).

R_f: 0.58 EtOAc 50%, Pet. Sp. 50%

IR: (Neat) 2930, 2855, 2228, 1609, 1577, 1495, 1464, 1448 cm⁻¹

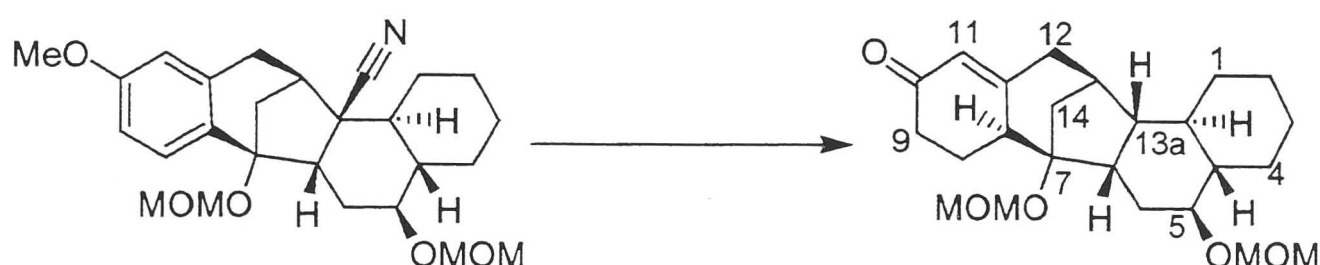
¹H NMR: (CDCl₃): 1.09-1.56 (m, 7H) 1.68-2.14 (m, 6H) 2.28 (dd, 1H, *J*=11.7 Hz, *J*=5.8 Hz, H14) 2.55 (m, 1H, H13) 2.79 (dd, 1H, *J*=13.4 Hz, *J*=4.1 Hz, H6a) 3.12 (m, 2H, H12) 3.34 (s, 3H, OCH₂OCH₃) 3.41 (s, 3H, OCH₂OCH₃) 3.57 (m, 1H, H5) 3.77 (s, 3H, OMe) 4.56-4.71 (m, 4H, OCH₂OCH₃) 6.68 (d, 1H, *J*=2.5 Hz, H11) 6.73 (dd, 1H, *J*=8.5 Hz, *J*=2.6 Hz, H9) 7.22 (d, 1H, *J*=8.5 Hz, H8)

¹³C NMR: (CDCl₃): 25.2 (CH₂), 26.0 (CH₂), 26.3 (CH₂), 29.0 (CH₂), 33.8 (CH₂), 34.9 (CH₂), 36.5 (CH₂), 39.6 (CH), 41.8 (CH), 42.4 (CH), 46.9 (C), 53.1 (CH), 54.9 (CH₃), 55.1 (CH₃), 55.6 (CH₃), 75.9 (CH), 83.7 (C), 92.7 (CH₂), 94.2 (CH₂), 112.4 (CH), 113.4 (CH), 122.1 (C), 123.8 (CH), 135.1 (C), 135.4 (C), 158.6 (C)

MS (EI) *m/z*: 441 (M⁺, 10%), 219 (100), 189 (38), 159 (22), 91 (6)

HRMS *m/z* calc'd for C₂₆H₃₅NO₅: 441.2515, found 441.2513

(4a*SR*,5*SR*,6a*SR*,7*SR*,7a*SR*,13*RS*,13a*RS*,13b*RS*)-5,7-bismethoxymethoxy-1,2,3,4,4a,5,6,6a,7,7a,8,9,12,13,13a,13b-Hexadecahydro-7,13-methano-10*H*-benzo[4,5]cyclohepta[1,2-*a*]-naphthalen-10-one (93)



Lithium metal (60 mg) was added in one portion to freshly distilled ammonia (150 ml) at -78°C and allowed to dissolve. Nitrile 86 (200 mg) was dissolved in THF (60 ml) and this solution was added to the stirred lithium solution. This was then allowed to warm to -33°C over 2 hours. Ethanol (2 ml) was added and the blue colour allowed to fade. Lithium metal (approx. 240 mg) was then added in portions so as to maintain the blue colour for 20 minutes after which time the ammonia was allowed to evaporate. The resulting solution is diluted with ethyl acetate (200 ml) and was washed with water (2x 200 ml) and brine (200 ml). The organic layer was then dried and the solvent removed *in vacuo* to give a white residue which contained methyl enol ether 92, which was immediately dissolved in THF (10 ml) and methanol (10 ml). To this stirred solution was added concentrated HCl (10 M, 30 μl) and stirring was continued for 45 minutes. The solution was then cooled to 0°C and quenched by the addition of aqueous sodium hydroxide solution (1M, 20 ml). This was extracted with ethyl acetate (3x 40 ml), the organic layers were then combined and washed with water (100 ml), brine (100 ml) and then dried and evaporated *in vacuo* to give an oily residue. This was purified by column chromatography (ethyl acetate/petroleum spirit 1:1) to give the pure α,β -enone as an oil that solidified on standing (100 mg, 55 %) and a mixture of the β,γ -enone **94** and its dimethoxy acetal **96** (61 mg).

R_f: 0.26 EtOAc 50%, Pet. Sp. 50%

IR: (Neat) 2925, 1670, 1619, 1447 cm^{-1}

^1H NMR: (CDCl_3): 0.69-1.01 (m, 4H), 1.06-1.32 (m, 4H), 1.62-1.96 (m, 7H), 2.00-2.23 (m, 6H), 2.25-2.43 (m, 2H), 2.80 (d, 1H, $J=8.5$ Hz, H7a), 3.27 (s, 3H, OCH_2OCH_3), 3.33 (s, 3H, OCH_2OCH_3), 3.40 (m, 1H, H5), 4.47 (d, 1H, $J=6.9$ Hz, OCH_2OCH_3), 4.59 (d, 1H, $J=7.0$ Hz, OCH_2OCH_3), 4.62 (d, 1H, $J=7.2$ Hz, OCH_2OCH_3), 4.73 (d, 1H, $J=7.0$ Hz, OCH_2OCH_3), 5.81 (s, 1H, H11)

^{13}C NMR: (CDCl_3): 22.0 (CH_2), 25.7 (CH_2), 26.1 (CH_2), 26.6 (CH_2), 32.6 (CH_2), 33.4 (CH_2), 35.8 (CH), 36.7 (CH_2), 37.9 (CH_2), 38.8 (CH), 42.8 (CH_2), 45.3 (CH), 46.8 (CH), 47.8 (CH), 55.0 (CH_3), 55.8 (CH_3), 77.4 (CH), 86.3 (C), 92.2 (CH_2), 94.3 (CH_2), 127.5 (CH), 163.3 (C), 198.9 (C)

MS (EI) m/z : 404 (M^+ , 5%), 342 (20), 298 (100), 280 (9), 201 (14), 188 (100), 161 (67), 135 (18), 110 (100), 91 (24), 67 (19)

HRMS m/z calc'd for $\text{C}_{24}\text{H}_{36}\text{O}_5$: 404.2563, found 404.2566

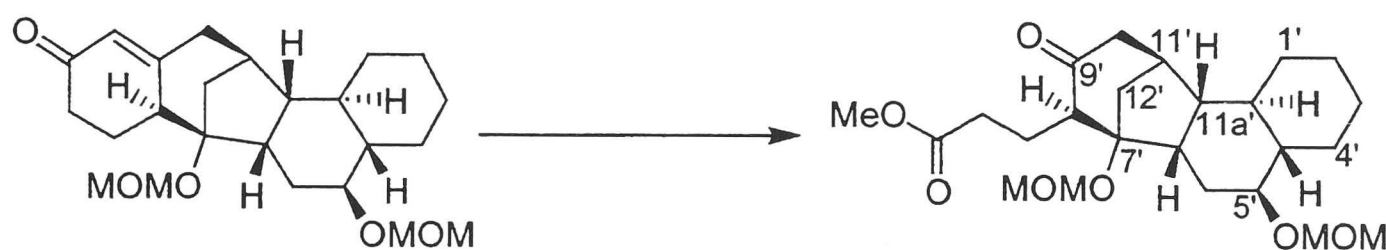
^1H NMR (for β,γ -enone-dimethoxy acetal (**96**)): (CDCl_3): 0.79-0.96 (m, 2H), 0.98-1.09 (m, 2H), 1.13-1.49 (m, 5H), 1.51-2.38 (m, 16H), 3.19 (s, 3H, OMe), 3.21 (s, 3H, OMe), 3.35 (s, 3H, OCH_2OCH_3), 3.37 (s, 3H, OCH_2OCH_3), 3.52 (m, 1H, H5), 4.50(d, 1H, $J=6.6$ Hz, OCH_2OCH_3), 4.53(d, 1H, $J=6.9$ Hz, OCH_2OCH_3), 4.61 (d, 1H, $J=6.6$ Hz, OCH_2OCH_3), 4.72 (d, 1H, $J=7.0$ Hz, OCH_2OCH_3),

Equilibration of the β,γ -enone-dimethoxy acetal 96 to the α,β -enone 93



The crude β,γ -enone-dimethoxy acetal 96 (300 mg) was dissolved in THF (20 ml) and methanol (20 ml). To this stirred solution was added aqueous HCl (30 μ l) and stirring was continued for 45 minutes. The solution was then cooled to 0°C and quenched by the addition of aqueous sodium hydroxide solution (1M, 20 ml). This was extracted with ethyl acetate (3x 40 ml), the organic layers were then combined and washed with water (100 ml), brine (100 ml) and then dried and evaporated *in vacuo* to give an oily residue. This was purified by column chromatography (ethyl acetate/petroleum spirit 1:1) to give the pure α,β -enone as an oil that solidified on standing (132 mg, 44%) and a mixture of the β,γ -enone and its dimethoxy acetal (156 mg).

Methyl-3-((4a'SR,5'SR,6a'SR,7'SR,7a'SR,8'RS,11'SR,11a'RS,11b'RS)-2',3',4',4a',5',6',6a',7',8',9',10',11',11a',11b'-tetradecahydro-5',7'-bismethoxymethoxy-9'-oxo-7',11'-methano-1'H-cyclohepta[a]naphthalen-8'-yl)-propanoate (103)



The enone **93** (60 mg) was dissolved in methanol (20 ml) and the solution was cooled to 0°C. Ozone (approx. 3-4% in O₂) was bubbled through the cooled solution until TLC had shown that all of the starting material had been consumed (approx. 1 h). The flask was flushed with N₂ for 15 minutes and then cooled to 0°C and dil. NaOH solution (1M, 10 ml) was added, followed by the dropwise addition of H₂O₂ (30% w/v, 2 ml) over 15 minutes. The reaction mixture was stirred for a further 45 minutes at 0°C and then stirred at room temperature for 2 hours. After this time the solution was diluted with EtOAc (30 ml) and then acidified to pH 2 with dil. KHSO₄ (1M) and saturated with solid NaCl. The organic layer was separated and the aqueous layer extracted with EtOAc (3x 20 ml). The organic layers were combined and washed with brine (2x 50 ml) and then dried and evaporated *in vacuo* to give the crude carboxylic acid **99**. The residue obtained was then dissolved in Et₂O (10 ml) and a solution of diazomethane in Et₂O was added dropwise until the yellow colour of diazomethane persisted in the solution. The reaction was then flushed with N₂ until the yellow colour was dissipated and the solvent removed *in vacuo* to give the crude compound, which was purified by column chromatography (ethyl acetate/petroleum spirit 1:1) to give the pure ester **103** (33 mg, 51%) as a clear oil.

R_f: 0.63 EtOAc 50%, Pet. Sp. 50%

IR: (Neat) 2926, 2851, 2822, 1738, 1709, 1440 cm^{-1}

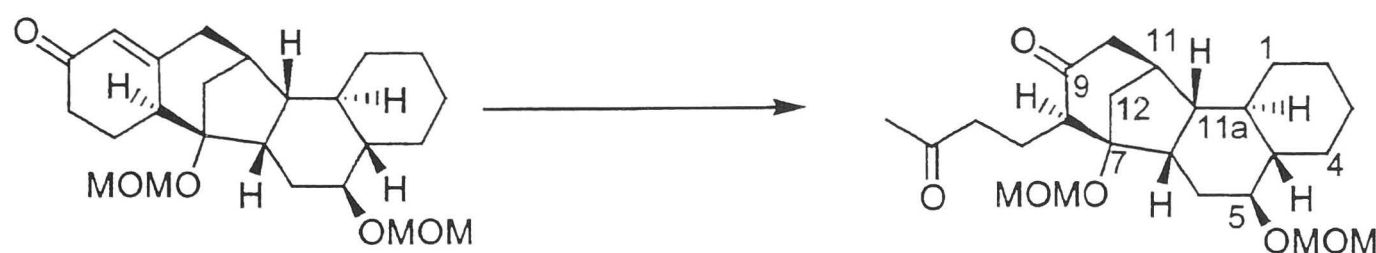
^1H NMR: (CDCl_3): 0.75-1.39 (m, 9H), 1.68-2.04 (m, 8H), 2.16-2.43 (m, 5H), 2.54-2.70 (m, 2H), 3.35 (s, 3H, OCH_2OCH_3), 3.39 (s, 3H, OCH_2OCH_3), 3.45 (m, 1H, H5), 3.64 (s, 3H, CO_2CH_3), 4.54 (d, 1H, $J=7.0$ Hz, OCH_2OCH_3), 4.67 (m, 2H, OCH_2OCH_3), 4.83 (d, 1H, $J=7.3$ Hz, OCH_2OCH_3)

^{13}C NMR: (CDCl_3): 18.4 (CH_2), 25.8 (CH_2), 26.2 (CH_2), 26.7 (CH_2), 32.6 (CH_2), 33.2 (CH_2), 33.6 (CH_2), 34.5 (CH), 36.9 (CH), 38.5 (CH_2), 39.1 (CH), 45.2 (CH), 48.1 (CH), 49.9 (CH_2), 51.5 (CH), 55.2 (CH_3), 56.0 (CH_3), 59.3 (CH_3), 77.5 (CH), 86.6 (C), 92.4 (CH_2), 94.6 (CH_2), 174.1 (C), 209.6 (C)

MS (EI) m/z : 377 (3%), 294 (82), 241 (13), 188 (100), 160 (28)

HRMS m/z calc'd for $\text{M.Na}^+ \text{C}_{24}\text{H}_{38}\text{O}_7\text{Na}$: 461.2515, found 461.2518

(4a*SR*,5*SR*,6a*SR*,7*SR*,7a*SR*,8*RS*,11*SR*,11a*RS*,11b*RS*)-8-(3'-oxobutyl)-1,2,3,4,4a,5,6,6a,7,8,10,11,11a,11b-Tetradecahydro-5,7-bismethoxymethoxy-7,11-methano-9*H*-cyclohepta[a]naphthalen-9-one (104)



The enone **93** (80 mg) was dissolved in THF (10 ml) and the resulting solution was cooled to -78°C . Methyl lithium (0.32 ml) was then added and the solution was stirred for 5 minutes at -78°C and then placed in an ice bath and stirred for an additional 1 hour after which the reaction was quenched by the addition of saturated NH_4Cl solution (5 ml). The reaction

was then extracted with ethyl acetate (3x 10 ml) and the organic layers combined and washed with water (20 ml), brine (20 ml) and then dried and evaporated *in vacuo* to give the crude allylic alcohol **98** which was used without delay. The allylic alcohol was dissolved in CH₃CN (5 ml) and CCl₄ (10 ml) and a phosphate buffer (NaH₂PO₄ (200 mg) and Na₂HPO₄ (600 mg) in water (10 ml)) was added followed by NaIO₄ (480 mg) in water (5 ml). The resulting solution was stirred vigorously and RuCl₃ (5 mg) in water (1 ml) was added. The reaction was stirred vigorously for 12 hours and diluted with water where necessary to dissolve any precipitate formed. After this time the solution was extracted with ethyl acetate (3x 70 ml), the organic layers were combined and washed with water (100 ml), brine (100 ml) and then dried and evaporated *in vacuo* to give the crude diketone which was purified by column chromatography (ethyl acetate/petroleum spirit 1:1) to give the pure diketone **104** (37 mg, 45%) as an oil.

R_f: 0.36 EtOAc 50%, Pet. Sp. 50%

IR: (Neat) 2927, 2852, 1743, 1713, 1445 cm⁻¹

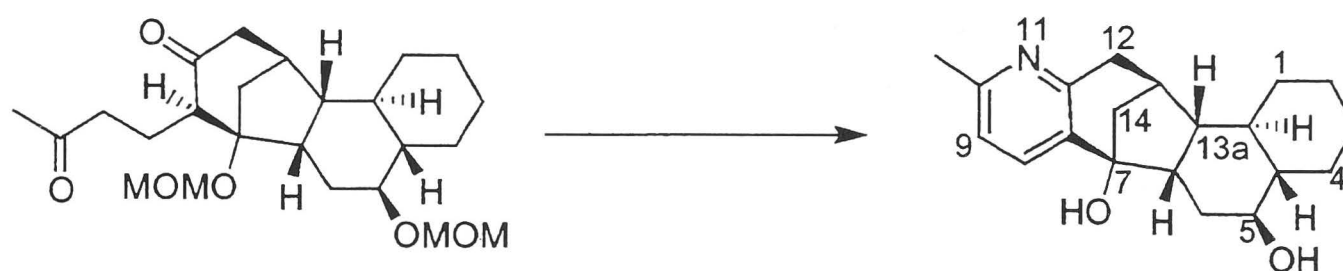
¹H NMR: (CDCl₃): 0.71-1.39 (m, 8H), 1.66-1.95 (m, 9H), 2.12 (s, 3H, COCH₃), 2.17-2.30 (m, 3H), 2.33-2.48 (m, 2H), 2.64 (t, 1H, *J*=5.8 Hz, H₈), 2.75 (dt, 1H, *J*=17.8 Hz, *J*=6.9 Hz), 3.35 (s, 3H, OCH₂OCH₃), 3.39 (s, 3H, OCH₂OCH₃), 3.46 (m, 1H, H₅), 4.54 (d, 1H, *J*=7.0 Hz, OCH₂OCH₃), 4.68 (m, 2H, OCH₂OCH₃), 4.85 (d, 1H, *J*=7.5 Hz, OCH₂OCH₃)

¹³C NMR: (CDCl₃): 17.1 (CH₂), 25.7 (CH₂), 26.7 (CH₂), 32.6 (CH₂), 33.5 (CH₂), 34.5 (CH), 36.8 (CH), 38.4 (CH₂), 39.0 (CH), 42.9 (CH₂), 45.1 (CH), 48.0 (CH), 49.9 (CH₂), 55.2 (CH₃), 55.9 (CH₃), 59.3 (CH), 77.4 (CH), 86.5 (C), 92.5 (CH₂), 94.5 (CH₂), 208.9 (C), 210.0 (C)

MS (EI) *m/z*: 422 (M⁺, 0.3%), 294 (64), 188 (100), 160 (31)

HRMS m/z calc'd for MH^+ $C_{24}H_{39}O_6$: 423.2747, found 423.2753

(4a*SR*,6a*SR*,7*SR*,13*RS*,13a*RS*,13b*RS*)-2,3,4,4a,5,6,6a,7,12,13,13a,13b-Dodecahydro-5,7-dihydroxy-10-methyl-7,13-methano-1*H*-naphtho[2',1':4,5]cyclohepta[1,2-*b*]pyridine (120)



The diketone **104** (10 mg) was dissolved in ethanol (3 ml) and $H_2NOH.HCl$ (5 mg) was added. The resulting solution was heated under reflux over night and then diluted with NaOH solution (1M, 10 ml) and extracted with EtOAc (4x15 ml). The organic layers were combined and washed with brine (40 ml) and then dried and evaporated *in vacuo* to give the nearly pure pyridine compound. This could be purified by column chromatography (ethyl acetate/methanol 20:1) to give the pure pyridine compound (7 mg, 95%) as a white solid.

R_f: 0.30 EtOAc 95%, MeOH 5%

1H NMR: ($CDCl_3$): 0.79-1.08 (m, 4H), 1.18-1.41 (m, 4H), 1.59-1.75 (m, 4H), 2.04 (m, 2H), 2.17 (m, 3H), 2.46 (s, 3H, CH_3), 2.70 (d, 1H, $J=17.4$ Hz, H12), 3.11 (dd, 1H, $J=17.3$ Hz, $J=3.8$ Hz, H12), 3.59 (m, 1H, H5), 7.08 (d, 1H, $J=7.9$ Hz, H9), 7.80 (d, 1H, $J=7.9$ Hz, H8)

^{13}C NMR: (CD_3OD): 22.3, 26.3, 26.8, 29.7, 33.4, 33.5, 36.3, 36.8, 39.9, 42.8, 45.9, 46.6, 50.7, 72.7 (CH), 78.6 (C), 121.2 (CH), 132.2 (CH), 141.6 (C), 153.8 (C), 155.6 (C)

MS (EI) m/z : 313 (M^+ , 5%), 160 (100)

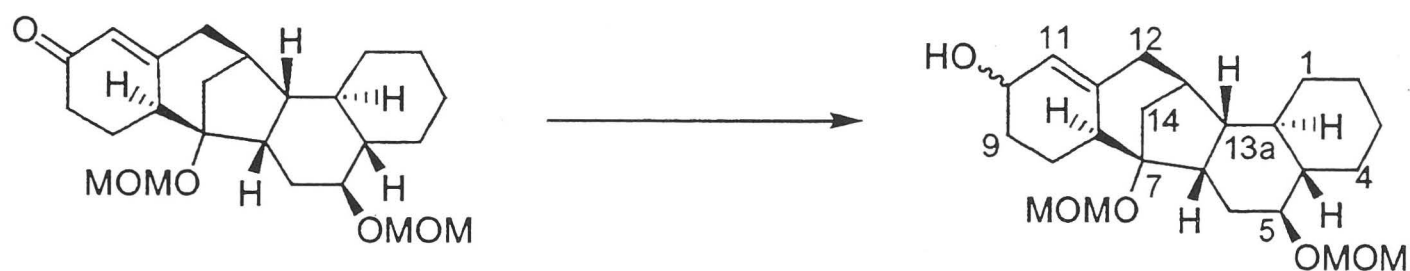
HRMS m/z calc'd for MH^+ $C_{20}H_{28}NO_2$: 314.2120, found 314.2124

(4a*SR*,5*SR*,6a*SR*,7*SR*,7a*SR*,13*RS*,13a*RS*,13b*RS*)-

1,2,3,4,4a,5,6,6a,7,7a,8,9,12,13,13a,13b-Hexadecahydro-5,7-

bismethoxymethoxy-7,13-methano-10*H*-benzo[4,5]cyclohepta[1,2-*a*]-

naphthalen-10-ol (110)



Lithium aluminium hydride (50 mg) was suspended in dry Et_2O (100 ml) and the solution cooled to $0^\circ C$. The enone **93** (400 mg) was dissolved in Et_2O (5 ml) and this solution was added slowly to the cooled LAH solution. The reaction was stirred for 30 minutes at $0^\circ C$ and then quenched by the slow addition of dil. $KHSO_4$ solution (1M, 30 ml). Water (100 ml) was added to the solution and then it was extracted with $EtOAc$ (3x 100 ml), the organic layers were combined and washed with water (200 ml) and brine (200 ml) and then dried and evaporated *in vacuo* to give the allylic alcohol **110** (400 mg) as a 5:1 mixture of diastereoisomers.

R_f : 0.40 $EtOAc$ 66%, Pet. Sp. 34%

IR: (Neat) 3429, 2925, 1662, 1446 cm^{-1}

1H NMR: ($CDCl_3$): 0.74-1.43 (m, 10H), 1.55-2.17 (m, 13H), 2.52 (m, 1H, H7a), 3.36 (s, 3H, OCH_2OCH_3), 3.37 (s, 3H, OCH_2OCH_3), 3.49 (m, 1H, H5), 4.22 (m,

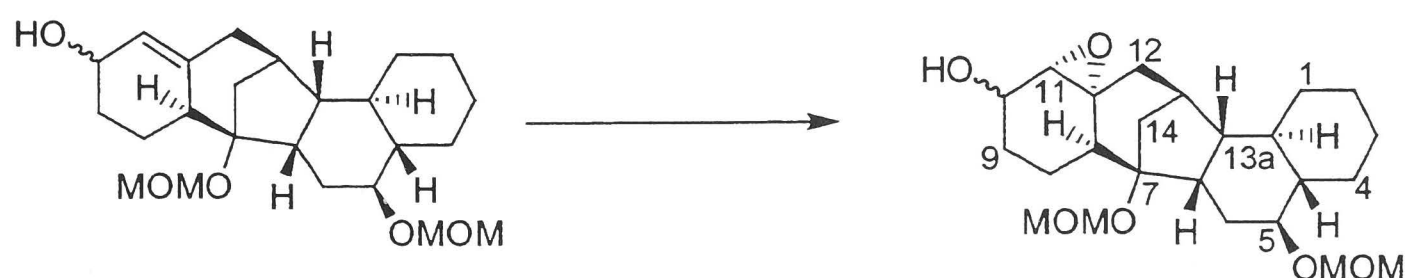
^1H , H10), 4.53 (d, 1H, $J=6.9$ Hz, OCH_2OCH_3), 4.60 (d, 1H, $J=6.9$ Hz, OCH_2OCH_3), 4.68 (d, 1H, $J=6.9$ Hz, OCH_2OCH_3), 4.77 (d, 1H, $J=6.9$ Hz, OCH_2OCH_3), 5.44 (s, 1H, H11)

^{13}C NMR: (CDCl_3): 25.8 (CH_2), 26.1 (CH_2), 26.7 (CH_2), 31.9 (CH_2), 32.6 (CH_2), 33.1 (CH_2), 33.5 (CH_2), 35.5 (CH), 36.1 (CH), 38.5 (CH_2), 38.6 (CH), 42.0 (CH_2), 45.3 (CH), 45.7 (CH), 47.7 (CH), 55.0 (CH_3), 55.5 (CH_3), 67.0 (CH), 77.7 (CH), 86.7 (C), 91.8 (CH_2), 94.2 (CH_2), 128.2 (CH), 138.3 (C)

MS (EI) m/z : 406 (M^+ , 0.04%), 312 (9), 295 (35), 282 (43), 189 (100), 173 (23), 161 (53), 145 (17), 135 (20), 94 (37), 79 (22)

(4a*SR*,5*SR*,6a*SR*,7*SR*,7a*RS*,13*RS*,13a*RS*,13b*RS*)-

1,2,3,4,4a,5,6,6a,7,7a,8,9,11,11a,12,13,13a,13b-Octadecahydro-11,11a-epoxy-5,7-bismethoxymethoxy-7,13-methano-10*H*-benzo[4,5]cyclohepta[1,2-*a*]-naphthalen-10-ol (111)



The allylic alcohol **110** (400 mg) was dissolved in DCM (100 ml) and a phosphate buffer of pH 6.5 (100 ml) was added, followed by *m*-CPBA (70-75%, 280 mg). The solution was stirred for 2 hours at room temperature, and then diluted with DCM (100 ml) and the organic layer separated and washed with dil. NaOH (100 ml), water (200 ml) and brine (200 ml) and then dried and evaporated *in vacuo* to give the epoxide (400 mg) as a mixture of 2 diastereoisomers.

R_f: 0.46 EtOAc 66%, Pet. Sp. 34%

IR: (Neat) 3436, 2923, 1445 cm⁻¹

¹H NMR: (CDCl₃): 0.72-0.88 (m, 2H), 0.98-1.39 (m, 8H), 1.46-1.79 (m, 7H), 1.81-2.07 (m, 5H), 2.28-2.39 (m, 2H), 3.11 (s, 1H, H11), 3.34 (s, 3H, OCH₂OCH₃), 3.36 (s, 3H, OCH₂OCH₃), 3.49 (m, 1H, H5), 3.94 (dd, 1H, *J*=9.9 Hz, *J*=4.5 Hz, H10), 4.55 (d, 2H, *J*=7.0 Hz, OCH₂OCH₃), 4.67 (d, 1H, *J*=6.9 Hz, OCH₂OCH₃), 4.71 (d, 1H, *J*=6.9 Hz, OCH₂OCH₃)

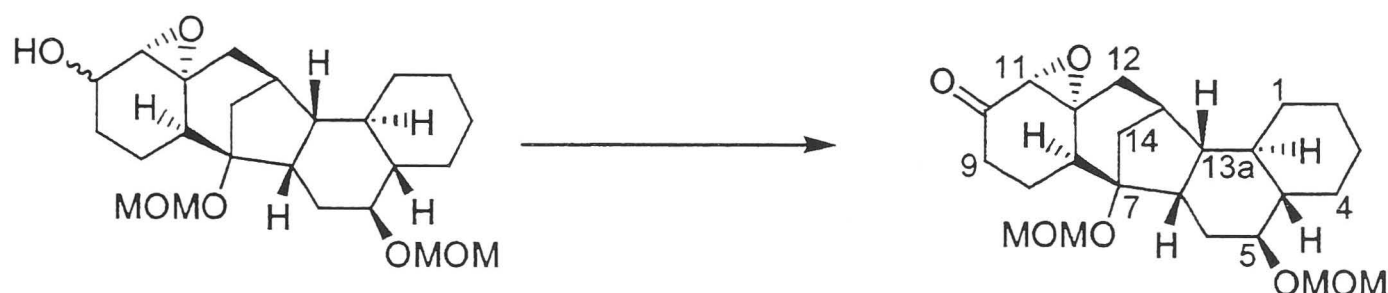
¹³C NMR: (CDCl₃): 21.9 (CH₂), 25.6 (CH₂), 25.8 (CH₂), 26.0 (CH₂), 26.6 (CH₂), 32.5 (CH₂), 33.3 (CH₂), 35.0 (CH), 36.1 (CH), 37.6 (CH₂), 38.8 (CH), 41.2 (CH), 42.4 (CH₂), 45.2 (CH), 47.1 (CH), 54.9 (CH₃), 55.6 (CH₃), 62.9 (C), 66.7 (CH), 68.6 (CH), 77.5 (CH), 86.1 (C), 91.7 (CH₂), 94.2 (CH₂)

MS (EI) *m/z*: 422 (M⁺, 0.02%), 298 (22), 254 (20), 189 (100), 161 (24), 135 (27), 91 (23), 79 (16)

HRMS *m/z* calc'd for MNa⁺ C₂₄H₃₈NaO₆: 445.2566, found 445.2577

(4aSR,5SR,6aSR,7SR,7aRS,13RS,13aRS,13bRS)-

1,2,3,4,4a,5,6,6a,7,7a,8,9,11,11a,12,13,13a,13b-Octadecahydro-11,11a-epoxy-5,7-bismethoxymethoxy-7,13-methano-10H-benzo[4,5]cyclohepta[1,2-a]-naphthalen-10-one (105)



The epoxy alcohol **111** (400 mg) was dissolved in DCM (100 ml) and solid NaHCO₃ (800 mg) was added, followed by Dess-Martin periodonane (600 mg). The solution was stirred at room temperature for 2.5 hours and then quenched by the addition of dil. Na₂S₂O₃ solution (1M, 100 ml), followed by stirring for 15 minutes. The resulting solution was diluted with DCM (100 ml) and the organic layer was separated and washed with water (200 ml) and brine 200 ml) and then dried and evaporated *in vacuo* to give the crude epoxy ketone. This was purified by column chromatography (ethyl acetate/petroleum spirit 1:1) to give the pure epoxy ketone (320 mg, 77% from the enone) as a single diastereoisomer.

R_f: 0.59 EtOAc 50%, Pet. Sp. 50%

IR: (Neat) 2927, 1717, 1445 cm⁻¹

¹H NMR: (CDCl₃): 0.70-0.88 (m, 2H), 0.95-1.10 (m, 2H), 1.11-1.38 (m, 6H), 1.59-2.12 (m, 11H), 2.25 (m, 1H, H₉), 2.68 (t, 1H, *J*=7.8 Hz, H_{7a}) 2.81 (m, 1H, H₉), 3.07 (s, 1H, H₁₁), 3.31 (s, 3H, OCH₂OCH₃), 3.34 (s, 3H, OCH₂OCH₃), 3.43 (m, 1H, H₅), 4.52 (d, 1H, *J*=6.9 Hz, OCH₂OCH₃), 4.60 (m, 2H, OCH₂OCH₃), 4.71 (d, 1H, *J*=7.0 Hz, OCH₂OCH₃)

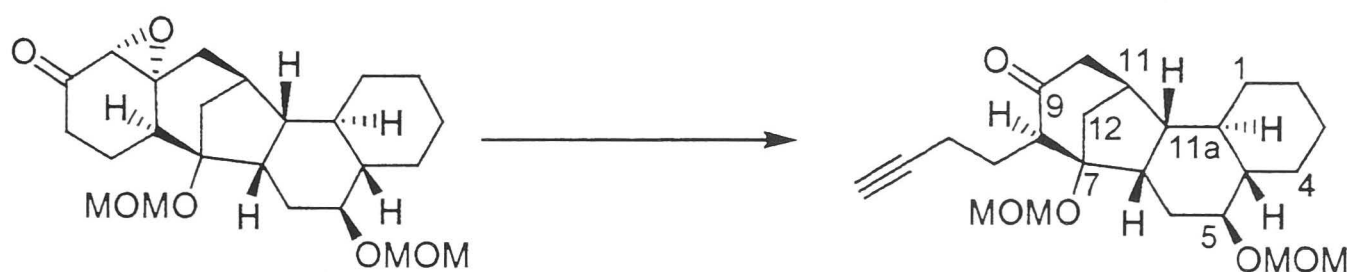
^{13}C NMR: (CDCl_3): 24.4 (CH_2), 25.9 (CH_2), 26.1 (CH_2), 26.5 (CH_2), 32.5 (CH_2), 33.3 (CH_2), 33.6 (CH_2), 34.9 (CH), 36.4 (CH), 37.6 (CH_2), 38.8 (CH), 41.7 (CH_2), 42.1 (CH), 45.0 (CH), 47.1 (CH), 55.0 (CH_3), 55.7 (CH_3), 64.2 (CH), 68.7 (C), 77.3 (CH), 85.9 (C), 92.0 (CH_2), 94.3 (CH_2), 207.9 (C)

MS (EI) m/z : 420 (M^+ , 1.5%), 314 (35), 286 (47), 268 (33), 189 (100), 161 (45), 135 (66), 91 (67), 67 (36)

HRMS m/z calc'd for $\text{C}_{24}\text{H}_{36}\text{O}_6$: 420.2512, found 420.2514

(4aSR,5SR,6aSR,7SR,7aSR,8RS,11SR,11aRS,11bRS)-

1,2,3,4,4a,5,6,6a,7,8,10,11,11a,11b-Tetradecahydro-8-(but-3'-ynyl)-5,7-bismethoxymethoxy-7,11-methano-9H-cyclohepta[a]naphthalen-9-one
(107)



The epoxy ketone 105 (60 mg) was dissolved in THF (2 ml) and ethanol (5 ml) and the solution cooled to -78°C . 4-nitrobenzenesulfonhydrazide (34 mg) was dissolved in THF (2 ml) and this solution was added to the cooled epoxy ketone. The resulting solution was placed in an ice bath and stirred for 1 hour. After this time pyridine (14 mg) was added, and the solution was allowed to warm to room temperature and the stirring was continued for a further 8 hours. The resulting yellow solution was diluted with sodium hydroxide solution (1M, 10 ml) and was then extracted with EtOAc (3x 15 ml). The organic layers were combined, washed with water (2x 25 ml), brine (25 ml) and then dried and evaporated *in vacuo* to give the crude alkynyl

ketone. This was purified by column chromatography (ethyl acetate/petroleum spirit 1:3) to give the pure alkynyl ketone as a clear oil that solidified on standing (44 mg, 76%).

R_f: 0.50 EtOAc 25%, Pet. Sp. 75%

IR: (Neat) 3284, 2927, 2115, 1708, 1446 cm⁻¹

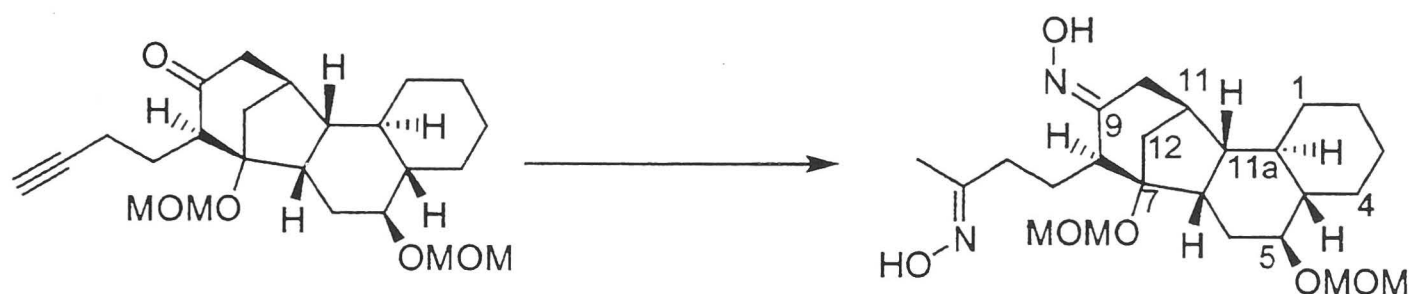
¹H NMR: (CDCl₃): 0.73-1.38 (m, 8H), 1.61-2.02 (m, 9H), 2.11-2.31 (m, 5H), 2.33-2.45 (m, 2H), 2.81 (d, 1H, *J*=9.1 Hz, H8), 3.32 (s, 3H, OCH₂OCH₃), 3.38 (s, 3H, OCH₂OCH₃), 3.43 (m, 1H, H5), 4.51 (d, 1H, *J*=6.9 Hz, OCH₂OCH₃), 4.62 (m, 2H, OCH₂OCH₃), 4.91 (d, 1H, *J*=7.3 Hz, OCH₂OCH₃)

¹³C NMR: (CDCl₃): 17.8 (CH₂), 21.6 (CH₂), 25.7 (CH₂), 26.2 (CH₂), 26.7 (CH₂), 32.6 (CH₂), 33.5 (CH₂), 34.6 (CH), 37.0 (CH), 38.6 (CH₂), 39.0 (CH), 45.1 (CH), 47.9 (CH), 49.8 (CH₂), 55.2 (CH₃), 55.9 (CH₃), 58.2 (CH), 68.6 (CH), 77.5 (CH), 84.6 (C), 86.2 (C), 92.0 (CH₂), 94.5 (CH₂), 209.7 (C)

MS (EI) *m/z*: 404 (M⁺, 0.2%), 294 (57), 188 (100), 160 (27), 135 (11), 84 (15), 67 (9)

HRMS *m/z* calc'd for C₂₄H₃₆O₅: 404.2562, found 404.2567

(4a*SR*,5*SR*,6a*SR*,7*SR*,7a*SR*,8*RS*,11*SR*,11a*RS*,11b*RS*)-8-(3'-(hydroxyimino)butyl)-1,2,3,4,4a,5,6,6a,7,8,10,11,11a,11b-Tetradecahydro-5,7-bismethoxymethoxy-7,11-methano-9*H*-cyclohepta[*a*]naphthalen-9-one oxime (121)



The alkynyl ketone 107 (35 mg) and hydroxylamine hydrochloride (20 mg) were dissolved in pyridine (1 ml) and the resulting solution was heated at 100°C for 4 hours. After this time the reaction was diluted with EtOAc (5 ml) and washed with dilute aqueous HCl (2 M) until all of the pyridine was removed from the organic layer. The aqueous layers were combined and extracted with EtOAc (2x 5ml) and the organic layers were then combined. The organic phase was then washed with water (15 ml) and brine (15 ml) and then dried and evaporated *in vacuo* to give the crude bisoxime which was used in the next step without further purification.

R_f: 0.68 EtOAc

IR: (Neat) 3368, 2926, 2851, 1790, 1730, 1653, 1446 cm⁻¹

¹H NMR: (CDCl₃): 0.79-0.87 (m, 2H), 1.00-1.36 (m, 7H), 1.68-1.78 (m, 4H), 1.83-2.02 (m, 5H), 1.94 (s, 3H, CNOHCH₃), 2.09-2.35 (m, 4H), 2.51-2.57 (m, 2H), 3.16 (d, 1H, *J*=15.2, H8), 3.36 (s, 3H, OCH₂OCH₃), 3.39 (s, 3H, OCH₂OCH₃), 4.11 (m, 1H, H5), 4.55 (d, 1H, *J*=6.9 Hz, OCH₂OCH₃), 4.67 (d, 2H, *J*=6.6 Hz, OCH₂OCH₃), 4.74 (d, 1H, *J*=7.2 Hz, OCH₂OCH₃)

^{13}C NMR: (CDCl_3): 13.9 (CH_3), 21.3 (CH_2), 26.2 (CH_2), 26.6 (CH_2), 27.1 (CH_2), 33.0 (CH_2), 34.0 (CH_2), 35.5 (CH), 35.6 (CH_2), 36.5 (CH), 38.7 (CH_2), 39.2 (CH), 45.5 (CH), 48.7 (CH), 51.0 (CH), 55.5 (CH_3), 56.2 (CH_3), 78.1 (CH), 86.5 (C), 92.6 (CH_2), 94.8 (CH_2), 159.1 (C), 159.3 (C)

MS (EI) m/z : 435($\text{M}^+ - \text{OH}$, 2%), 398 (3), 356 (100), 256 (49), 204 (24), 182 (26), 132 (17), 104 (30), 75 (27)

N-Acetoxy-(4a*SR*,5*SR*,6a*SR*,7*SR*,7a*SR*,10*RS*,11a*SR*,13*RS*,13a*RS*,13b*RS*)-2,3,4,4a,5,6,6a,7,7a,8,9,10,11,11a,12,13,13a,13b-octadecahydro-5,7-bismethoxymethoxy-10-methyl-7,13-methano-1*H*-naphtho[2',1':4,5]cyclohepta[1,2-*b*]pyridine (125)



To a solution of NaBH_4 (11 mg) in THF (5 ml) was added ZrCl_4 (17 mg) and this suspension was stirred vigorously for 10 minutes. To the resulting white suspension was added the bisoxime 121 (20 mg) and the reaction was stirred for 16 hours at r.t. After this time the reaction was quenched by the slow addition of dilute sodium hydroxide (5 ml) and then it was extracted with EtOAc (3x 10 ml). The organic layers were combined and washed with water (20 ml) and brine (20 ml) and then dried with sodium sulfate and evaporated *in vacuo* to give the crude *N*-hydroxypiperidine compound 124. This was dissolved in acetic anhydride (1 ml) and pyridine (1 ml) and the reaction stirred for 3 hours. The solvent was removed *in vacuo* and the residue obtained was dissolved in EtOAc (10 ml) and washed with dilute HCl (5 ml), water (5 ml), dilute sodium hydroxide (5 ml), water (5 ml) and

brine (10 ml) and then dried and evaporated *in vacuo*. The crude mixture was then purified by column chromatography (ethyl acetate/petroleum spirit 1:3) to give the pure *N*-acetoxypiperidine **125** (7 mg, 30%) as a clear oil.

R_f: 0.67 EtOAc 50%, Pet. Sp. 50%

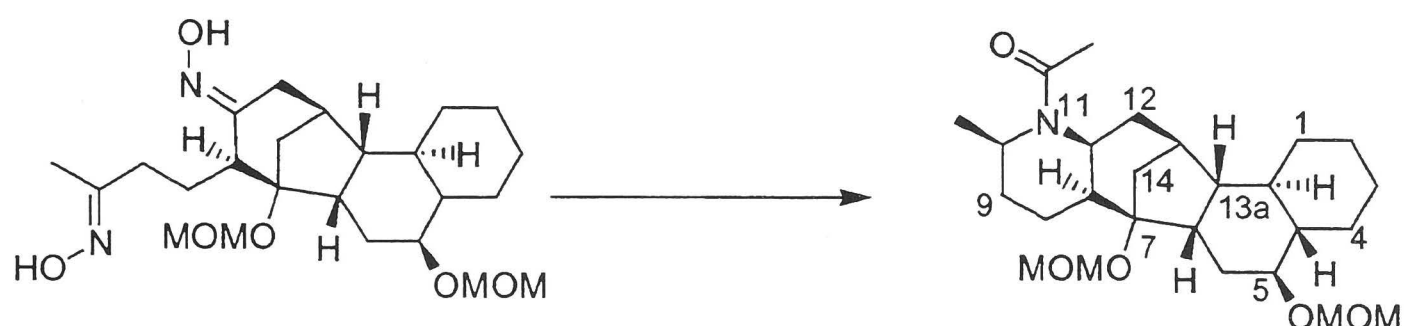
IR: (Neat) 2922, 2851, 1765, 1732, 1447 cm⁻¹

¹H NMR: (500 MHz, CDCl₃): 0.72 (qd, 1H, *J*=11.2 Hz, *J*=3.4 Hz, H13b), 0.84-1.04 (m, 2H, H1, H4), 1.06 (d, 3H, *J*=6.0 Hz, H10'), 1.04-1.22 (m, 2H), 1.24-1.36 (m, 3H, H6, H8, H14), 1.48 (ddd, 1H, *J*=14.7 Hz, *J*=5.8 Hz, *J*=2.8 Hz, H12), 1.56 (m, 1H, H9), 1.63-1.72 (m, 3H), 1.74-1.87 (m, 4H), 1.89-1.97 (m, 2H, H4, H13), 2.04 (s, 3H, CH₃CO₂), 2.06 (m, 1H, H14), 2.24 (dm, 1H, *J*=14.5 Hz, H8), 2.34 (t, 1H, *J*=6.4 Hz, H7a), 2.55 (m, 1H, H10), 2.64-2.77 (m, 2H, H6a, H13a), 3.12 (t, 1H, *J*=6.0 Hz, H11a) 3.39 (s, 3H, OCH₂OCH₃), 3.40 (s, 3H, OCH₂OCH₃), 3.50 (m, 1H, H5), 4.59 (d, 1H, *J*=6.9 Hz, OCH₂OCH₃), 4.66 (s, 2H, OCH₂OCH₃), 4.74 (d, 1H, *J*=6.9 Hz, OCH₂OCH₃)

¹³C NMR: (125 MHz, CDCl₃): 19.4 (CH₃), 20.5 (CH₃), 22.3 (CH₂), 26.4 (CH₂), 26.45 (CH₂), 26.7 (CH₂), 31.4 (CH₂), 32.5 (CH₂), 34.0 (CH₂), 34.5 (CH₂), 36.7 (CH), 38.1 (CH) 39.2 (CH₂), 39.3 (CH), 44.1 (CH), 44.8 (CH), 45.9 (CH), 55.1 (CH₃), 55.9 (CH₃), 63.4 (CH), 65.5 (CH), 78.1 (CH), 85.9 (C), 92.2 (CH₂), 94.3 (CH₂), 171.9 (C)

MS (EI) *m/z*: 406 (M⁺-CH₃CO₂, 81%), 360 (100), 298 (54), 208 (17), 189 (11), 111 (14)

N-Acetyl-(4a*SR*,5*SR*,6a*SR*,7*SR*,7a*SR*,10*RS*,11a*SR*,13*RS*,13a*RS*,13b*RS*)-2,3,4,4a,5,6,6a,7,7a,8,9,10,11,11a,12,13,13a,13b-octadecahydro-5,7-bismethoxymethoxy-10-methyl-7,13-methano-1*H*-naphtho[2',1':4,5]cyclohepta[1,2-*b*]pyridine (131)



To a solution of NaBH_4 (28 mg) in THF (20 ml) was added ZrCl_4 (42 mg) and this suspension was stirred vigorously for 10 minutes. To the resulting white suspension was added the bisoxime 121 (50 mg) and the reaction was stirred for 16 hours at r.t. After this time, the reaction was quenched by the slow addition of dilute sodium hydroxide (10 ml) and then it was extracted with EtOAc (3x 10 ml). The organic layers were combined and washed with water (20 ml) and brine (20 ml) and then dried with sodium sulfate and evaporated *in vacuo* to give the crude *N*-hydroxypiperidine compound 124. The crude *N*-hydroxypiperidine compound was dissolved in acetic acid (1 ml) and zinc dust (100 mg) was added. The resulting suspension was stirred at room temperature for 4 hours and then diluted with EtOAc (10 ml) and filtered to remove the zinc dust. The solution was then made basic with aqueous NaOH solution (10 M) and then extracted with EtOAc (3x20 ml). The organic layers were combined and washed with water (30 ml), brine (30 ml) and then dried with sodium sulfate and evaporated *in vacuo* to give the crude piperidine compound 130. This was dissolved in acetic anhydride (1 ml) and pyridine (1 ml) and the reaction stirred for 3 hours. The solvent was removed *in vacuo* and the residue obtained was dissolved in EtOAc (10 ml) and washed with dilute HCl (5 ml), water (5 ml), dilute sodium hydroxide (5 ml), water (5 ml) and brine (10 ml) and then dried and evaporated *in vacuo*.

The crude mixture was then purified by column chromatography (ethyl acetate/methanol 98:2) to give the pure *N*-acetylpiperidine **131** (16 mg, 29% for the four steps from **107**) as a clear oil.

R_f: 0.22 EtOAc 100%

IR: (Neat) 2924, 2845, 1638, 1446, 1416 cm⁻¹

¹H NMR: 0.69-0.91 (m, 3H), 1.24 (d, 3H, *J*=7.2 Hz, H10'), 0.98-1.42 (m, 8H), 1.57-1.84 (m, 8H), 1.88-2.04 (m, 3H), 2.11 (s, 3H, COCH₃), 2.36 (m, 1H), 2.53 (m, 1H), 3.35 (s, 3H, OCH₂OCH₃), 3.39 (s, 3H, OCH₂OCH₃), 3.56 (m, 1H, H5), 4.01 (m, 1H, H10), 4.54-4.60 (m, 2H, OCH₂OCH₃), 4.72 (d, 1H, *J*=7.0 Hz, OCH₂OCH₃), 4.76-4.85 (m, 2H, H11a, OCH₂OCH₃)

¹³C NMR: 17.7 (CH₃), 20.6 (CH₃), 22.3 (CH₂), 26.2 (CH₂), 26.3 (CH₂), 26.8 (CH₂), 29.2 (CH₂), 30.5 (CH₂), 33.2 (CH₂), 33.7 (CH₂), 34.6, 34.65, 35.0, 39.9 (CH), 44.3 (CH), 45.0 (CH), 45.5 (CH), 48.0 (CH), 54.2 (CH), 55.3 (CH₃), 55.6 (CH₃), 78.3 (CH), 85.9 (C), 93.0 (CH₂), 94.6 (CH₂), 169.7 (C)

MS (EI) *m/z*: 449 (M⁺, 45%), 404 (48), 388 (91), 358 (23), 342 (57), 326 (44), 300 (33), 252 (46), 204 (47), 154 (45), 140 (100), 107 (55), 67 (44)

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Notes and corrections

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Erratum

Page 13, scheme 1.8: 5th reagent combination AcOH, Py should be Ac₂O, Py

Page 32, scheme 2.9: ⁿBu₄B should be ⁿBu₄NBr

Page 42, line 16: eluant should be eluent

Page 50, line 17: 1,2 alkyl shift should read 1,2 aryl shift

Page 51, line 1: The three AB systems should read The one AB and two ABX systems

Page 73, line 10: dihyroxylate should be dihydroxylate

Page 84, line 4: tosyl hydrazide should read tosyl hydrazone

Page 85, line 8 and 9: Baeyer-Villager should read Baeyer- Villiger

Page 124, line 9: methanol should be water

Page 124, line 16: distallation should be distillation